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EJNAR MUNKSGAARD · COPENHAGEN

FROM THE UNIVERSITY CLINIC OF PSYCHIATRY, RIGSHOSPITALET, COPENHAGEN, DENMARK (PROFESSOR VILLARS LUNN)

HYPERTHERM TREATMENT OF NEUROSYPHILIS

Methods of evaluation and prognostically important factors.

By

KAJ ARENTSEN and JOSEPH WELNER

After *Kettering*'s hypertherm on *Boas*' initiative began to be used in Denmark in 1942, an animated discussion arose as to the question whether it was justifiable to give up malarial treatment of neurosyphilis. The efficiency of the latter had long been established, from Danish quarters amongst others by *Lomholt* (1944) and *Madsen* (1949); but when the provisional results of hypertherm treatment were submitted by *Boas* (1949) they seemed completely satisfactory, and hypertherm treatment was therefore used in this clinic as a routine method, the more so as this therapy offers obvious advantages to the malarial treatment: controllable hyperthermia, less risk, fewer secondary effects, and a possibility of out-patient treatment. The last-mentioned circumstance highly facilitates the possibility of having the patients treated at an early stage of the disease.

When after World War II the penicillin treatment of neurosyphilis came to be known in this country and the information was very encouraging, this therapy was started in the clinic and has since then been used alongside of hypertherm treatment, the two treatments being given now alternately, now simultaneously. After 1947 hypertherm treatment has extremely rarely been used isolatedly. Very few patients have been treated with penicillin only.

The reasons for this procedure have partly been that the results of hypertherm treatment so far were so good that only demonstrably still more effective methods of treatment ought to replace it, partly that the communications about the effect of penicillin upon neurosyphilis were so encouraging that it was not deemed allowable to disregard them. Finally, it was to be hoped that it was possible to obtain an intensified effect by combining the two forms of treatment.

However, the communications about the effectivity of isolated penicillin treatment during recent years have been still more encouraging, for which reason the question of the seasonableness of completely giving up hypertherm treatment must arise, the more so as by changing to penicillin treatment we should obtain all chances of instituting an early, out-patient, and safe therapy.

The purpose of the present work therefore has been by an analysis of the results of our treatment to try to establish whether the hypertherm treatment bears comparison with other forms of treatment of neurosyphilis; furthermore whether the combination of penicillin and hypertherm treatment means further progress, and finally whether isolated treatment with penicillin is so effective a therapy that it will be reasonable to abandon the fever therapy of neurosyphilis.

Furthermore, we have by these investigations obtained an insight into a few of the factors which—besides the treatment—are determinative of the prognosis or, respectively, may offer some indication for re-treatment.

MATERIAL AND METHOD

During the years 1943–53 a total of 369 patients have been treated for neurosyphilis in this clinic. This material cannot on the face of it be expected to be representative of neurosyphilis in Denmark during the period in question. Our clinic, indeed, receives patients from the whole country, but especially during the first years some patients with particularly severe psychic symptoms have been referred directly to the mental hospitals. Inversely, a considerable number of patients with mild or absent psychic symptoms have been treated outside psychiatric departments and mental hospitals.

In order as many-sidedly as possible to compare our material with that of other authors we have attached importance to the fact that the patients before treatment should be suffering from an active neurosyphilitic process and be well-controlled during the following years by the clinic's own staff. So we have made a demand to our material that before as well as at least six months after treatment a psychiatric-neurological examination should have been made, an evaluation of the working capacity of the patients, and finally an examination of the cerebrospinal fluid. This demand was fulfilled by 194 patients only, as 138 patients must be omitted because of defective control; 20 had died within 6 months after the first treatment, 13 had previously been treated so thoroughly and specifically for their neurosyphilis that the cerebrospinal fluid was normalized before they came under our treatment. As, furthermore, these 13 patients had not during the whole

observation period shown any signs of clinical or humoral progression, it was necessary to describe them as cured with defect, and therefore they have been left out of our material. Two patients had during the observation period been subjected to malarial treatment elsewhere, and another two patients were left out because of complicating disorders which made it impossible to decide the importance of their neurosyphilis for their clinical condition.

Because of these facts we have in our material fewer patients with severe psychic symptoms than in statements from mental hospitals, e.g. *Lomholt* (1944), while, in spite of this fact, it appears that our material as regards diagnostic grouping corresponds quite well to greater representative foreign papers (*Curtis* (1950), *Callaway et al.* (1950)).—It is uncertain whether our material is comparable with the latter materials as regards the gravity of the psychic symptoms. However, a difference in the gravity of the psychic symptoms need not compromise the comparability, as *Callaway et al.* (1950) have called attention to the fact that the effect of treatment is independent of it, as also proved to be substantiated by our investigations. Furthermore, the method chosen by us for a determination of the effectivity of treatment should eliminate such a difference.

Of the 194 patients entering into our investigations, 5 suffered from congenital syphilis, the rest from acquired syphilis. In two thirds of the cases the time of infection could not be stated and only 108 patients had in the primary or secondary stage obtained an—often insufficient—treatment.

63 patient had been treated after the neurosyphilitic symptoms had manifested themselves, but only 40 of these had previously been given a specific treatment directed towards their neurosyphilis (6 penicillin, 17 malarial treatment, and 17 other fever therapy). These patients—as distinct from those cured with defects—have been included in the investigations because on applying to the clinic they showed clinical or humoral symptoms of active neurosyphilis.

Distribution According to Age.

< 20 years: 1	30–39 years: 28	50–59 years: 66
20–29 years: 7	40–49 years: 80	60–69 years: 12

133 patients were men and 51 patients were women.

The duration of the neurosyphilitic symptoms before treatment was less than 6 months in 41 of our patients, between 6 and 12 months in 14, 1–3 years in 45, 3–5 years in 11, more than 5 in 31, and uncertain in 52.

The number of patients suffering from the various types of neurosyphilis were as follows:

General paresis	90
Taboparesis	43
Tabes dorsalis	19
Meningovascular syphilis	29
Senile form	1
Asymptomatic neurosyphilis	11
Unclassifiable	1

In our material there are thus 133 patients suffering from paresis, who according to the psychiatric picture can be grouped as follows:

Neurasthenic, slightly demented	63
Euphoric, fatuously demented	60
Expansively megalomaniac	3
Delusional-hallucinatory	1
Manic-depressive	2
Delirious type	2
Unclassifiable	2

Thus only about one third of our total material of patients offers fairly severe psychopathological symptoms. In accordance with this fact 78 of our 194 patients were fit for work and 20 in part fit before treatment.

The patients included in the material have been observed for fairly varying periods. On the part of the clinic it has been endeavoured to have them appear for control every six months or every year. We succeeded in this to a wide extent, but in the case of some patients a fairly long period passed between the first treatment and the control examination.

At the evaluation of the effect of the treatment we have in the tables below and the calculations made on the basis of them selected the following two times as suitable to illustrate the effect of the treatment:

(1) The *first clinical, social,* and *humoral* examination at least six months following the first series of treatments. The average period for this observation series is *15* months; 27 patients have been observed for more than two years.

(2) The *last clinical, social,* and *humoral* examination after the *complete* treatment. The average period for this observation series is *4–5* years. The range is considerable; thus 37 patients have been observed for less than two years and eight patients for more than ten years.

20 patients have as first treatment been given penicillin only and 17 patients have during the whole period of observation had no other treatment. These materials are partly too small for independent investigation, partly too selected, as the indication for isolated treatment with penicillin has at our clinic mainly been a counter-indication for hypertherm treatment. Therefore they are left out of the comparative investigations of the effect of the treatment, but are included in the analysis of the prognosis, of which an account will be given at the end of this article.

In a preliminary investigation the results furthermore proved to be the same whether penicillin was administered simultaneously or alternately with hypertherm treatment, and all the patients who have undergone hypertherm as well as penicillin treatment have therefore been included in one group, which will be termed *combined treatment* in what follows.

In this way the groups of patients which will be made the object of more detailed investigation will be the following:

(1) 174 patients who at our clinic have each undergone one series of treatments, thus in the case of 101 patients hypertherm treatment, and in the case of 73 patients combined treatment. The period of observation was at least 6 months, the average being 15 months.

(2) 177 patients who in the case of 58 patients have undergone hypertherm treatment and in the case of 119 patients combined treatment. The period of observation was on an average 4–5 years, but with a very wide range. The majority of the patients have undergone repeated series of treatments, retreatment having been given to a very great extent. The indication for this has been given by a total estimate of the clinical, social, and humoral aspects of the condition, so that retreatment has been instituted if only one of these aspects seemed unsatisfactory. A good number of patients have therefore been retreated, even though their cerebrospinal fluid was restored.

The treatment given thus was very ample as compared with the indications of the literature.

A series of hypertherm treatments has consisted of about 10 single treatments, i.e. at least 30 hours with a body temperature of 40° C. or more. A single cure has lasted about five weeks. A few patients, however, have undergone 20–40 or even more treatments in a single series and during the whole period of observation six patients have undergone more than 40 treatments. The technique used has been described by *Boas* (1942).

A series of penicillin treatments has been of at least 6 million, as a rule 10 million, and in a few cases up to 48 million units of penicillin. A single cure generally lasted 18–21 days. During the period of observation as a whole, very large doses have been administered, thus in the case of 16 patients more than 48 million units of penicillin.

In order to be able to evaluate statistically the results obtained by our in-

vestigations, we have used the χ^2-method for comparison of the distributions observed, as described by *Kemp* (1942). The P-value found have in the present paper been evaluated and denoted in the following way: $0.05 < P$: insignificant. $0.01 < P < 0.05$: slightly significant. $0.001 < P < 0.01$: highly significant, and $P < 0.001$: very highly significant.

EFFECT OF THE TREATMENT ON THE MATERIAL OF PATIENTS AS A WHOLE

The changes which by virtue of the treatment take place in the case of the material as a whole, are indicated in *Table 1*, where the displacements before and after the two forms of treatment have been made up for a period of observation of averagely 15 months and 4–5 years. Both a clinical, a social, and a humoral standard have been used.

At the clinical evaluation in the form of a distinction between symptom-free, improved, and unchanged and aggravated, special importance has been attached to statements made by the relatives and concordant opinions of several clinicians.

At the social judgment we only denoted as fit those patients who were completely fit for work within their previous occupation. If this was not so, they have only been included in the group of partly fit.

At the humoral judgment we have partly marked the effect on the various qualities of the cerebrospinal fluid, partly marked the effect on a combination of these. A limit has been set up at a cell-count of $\leq$ 12/3 cells per cu. mm, and an amount of total protein of $\leq$ 20 ("Bisgaard units"), these values having been used as a normality criterion by *Lomholt* (1944) and in the case of the cell-count by *Dattner* (1951). A conversion of "Bisgaard units" in the case of the protein content is unfortunately impossible (*Munk Plum* (1954)); so it has not been possible on this point to make a comparison with papers by foreign authors. By a normal cerebrospinal fluid we understand a cerebrospinal fluid with values below or on the limits indicated, whereas the Wassermann reaction (WaR) has not been considered.

At the evaluation of the effect of the treatment we have been obliged to consider the fact that severe symptoms are relatively little prominent in our material. At the calculation of the effect we have therefore in the case of the clinical evaluation deducted the asymptomatic forms; in the case of the social evaluation we have deducted the patients who were fit beforehand, and finally we have, when humoral criteria were used as basis of our evaluation, deducted the patients in whom the qualities of the cerebrospinal fluid were below the boundaries of normality stated.

Period of observation 15 months: 20 per cent. (33 out of 164) have

become symptom-free, 75 per cent. (123 out of 164) have become symptom-free or have improved. 44 per cent. (47 out of 108) have become fit. At the examinations of the cerebrospinal fluid it was found that the cell-count became normal in 72 per cent. (102 out of 141), and that the amount of total protein became normal in 72 per cent. (77 out of 107). The WaR became negative in 18 per cent. (30 out of 165), and finally the cerebrospinal fluid as a whole was normalized in 65 per cent. (100 out of 153).

Period of observation 4–5 years: 30 per cent. (50 out of 167) have become symptom-free. 74 per cent. (123 out of 167) have become symptom-free or have improved. 40 per cent. (44 out of 110) have befit. At the examinations of the cerebrospinal fluid it was found that the cell-count became normal in 91 per cent. (121 out of 133), and the amount of total protein became normal in 68 per cent. (73 out of 108). The WaR became negative in 41 per cent. (69 out of 168), and finally the cerebrospinal fluid was normalized in 70 per cent. (109 out of 156).

The most striking feature about this comparison is the small difference between the results at the two periods of observation apart from the fact that the WaR in the cerebrospinal fluid is negative only in 18 per cent. at a period of observation of 15 months as against 41 per cent. after a period of 4–5 years, a fact which is in good agreement with that often observed, e.g. by *Dattner* (1950 and 1951), that the complement-fixation test in the case of any form of antisyphilitic treatment is normalized late and later than other symptoms. In this connexion it should be emphasized that the patients between the two times of observation in the great majority of the cases were under intensive and prolonged treatment.

The relations between the various criteria and their importance as indicators of active processes and hence for retreatment will be subjected to closer investigation below.

HYPERTHERM TREATMENT AS COMPARED WITH COMBINED TREATMENT

Period of Observation 15 months: As appears from *Table 1*, the difference between the two forms of treatment as a whole is small. The percentages—the patients who before the first treatment were symptom-free, fit for work, and had normal cerebrospinal fluids, respectively, being disregarded in order to retain the comparability—are close to one another.

In order to evaluate these differences the χ^2-method has been used. It is found that pure hypertherm treatment apparently has a somewhat

TABLE 1

			Clinical evaluation			Social evaluation			Humoral evaluation									Number of patients
									Cells			Total prot.		Wa R			Total eval.		
			Sympt. free	Unchanged or aggrav.	Improved	Fit	Partly fit	Disabled	≤ 12/3	13/3–19/3	≥ 20	≤ 20	> 20	÷	±	+	Normal	Pathol.	
First re-examination Obs. period ab. 15 months	Hyperthermia	before	5			40	12	49	24	9	68	49	52	8	7	86	18	83	101
		after	30	48	23	65	10	26	82	5	14	92	9	28	31	42	80	21	
	Comb. treatm.	before	5			26	7	40	9	4	60	18	55	1	4	68	3	70	73
		after	13	42	18	48	10	15	53	13	7	52	21	11	17	45	41	32	
	In all	before	10			66	19	89	33	13	128	67	107	9	11	154	21	153	174
		after	43	90	41	113	20	41	135	18	21	144	30	39	48	87	121	53	
Last re-examination Obs. period 4-5 years	Hyperthermia	before	1			23	6	29	15	5	38	29	29	5	5	48	12	46	58
		after	27	21	10	41	5	12	51	4	3	52	6	33	15	10	48	10	
	Comb. treatm.	before	9			44	14	61	19	8	92	40	79	4	6	109	9	110	119
		after	33	52	34	70	16	33	104	10	5	90	29	45	49	25	82	37	
	In all	before	10			67	20	90	34	13	130	69	108	9	11	157	21	156	177
		after	60	73	44	111	21	45	155	14	8	142	35	78	64	35	130	47	

Results of treatment for the material of patients as a whole in relation to clinical, social, and humoral criteria. The results are made up after 15 months as well as after 4–5 years, and in relation to the two methods of treatment. The figures indicate the number of patients showing the quality in question at a definite time after treatment. See further the text.

better effect than the other methods when clinical criteria are used as basis. The difference, however, is only slightly significant ($0.02 < P < 0.05$). If social criteria are used as basis of the evaluation, the difference is insignificant ($0.1 < P$). If humoral criteria are used as basis, we find no difference in the case of the cell-count ($0.1 < P$), but in the case of the amount of total protein we find a slightly better effect of pure hypertherm treatment ($0.01 < P < 0.02$). As to the total cerebrospinal fluid we find a highly significant difference in favour of the pure hypertherm treatment ($0.001 < P < 0.01$).

This paradoxical fact will be discussed in detail below.

Period of observation 4–5 years: When clinical criteria are used as basis of the evaluation, it is found that pure hypertherm treatment in these materials gives better results than combined treatment ($0.001 < P < 0.01$), thus a highly significant difference.—When social criteria are used as basis, however, we find no difference between the two materials ($0.1 < P$), and finally, as regards the cerebrospinal fluid we find quite uniform results in the case of the cell-count ($0.1 < P$). The capability of the two therapies to reduce the total protein content ≤ 20 is also the same ($0.1 < P$), and finally it appears that the number of normalized cerebrospinal fluids in the two forms of treatment is without any statistically significant difference ($0.1 < P$).

We are not of opinion that the—statistically significant—differences found allow us to conclude that hypertherm treatment should have a better effect than combined treatment.

The prognosis is complexly conditioned and the kind of the treatment is only one of the factors determining it.

It may, however, be shown that the materials compared are completely alike as regards age, diagnostic grouping, duration of the neurosyphilitic symptoms, and the kind and dose of the preceding treatment. On the other hand there are two factors which compromise the comparability.

First, the abnormalities of the cerebrospinal fluid in the hypertherm material (with a period of observation of 15 months) are on an average a little less pronounced than those in the other material. Thus we find in this material 67 per cent. with a cell-count $> 20/3$ per cu. mm and 52 per cent. with an amount of total protein > 20 as against 82 and 75 per cent., respectively, in the material which has undergone combined treatment. This explains the fact that the first hypertherm treatment can restore a greater number of the pathological cerebrospinal fluids.

Secondly, the hypertherm material (with a period of observation of 4–5 years) is biased for reasons of medical history, as this group

of patients to a great extent has come to consist of those patients who after 1947, when penicillin treatment was introduced into Denmark, did not need any treatment. The hypertherm material just includes a considerable number of patients with a very long period of observation who have been cured with a greater or smaller defect. This explains why the number of cured patients is greater than in the material undergoing combined treatment. The possibility of a somewhat too optimistic evaluation on the part of the clinicians must be held open, considering that the effect of the two forms of treatment upon working capacity and cerebrospinal fluid is quite the same.

The reason why at an observation period of an average of 15 months we also find a slightly better effect of hypertherm treatment according to the evaluation by the clinicians is presumably that there has not been a sufficiently sharp distinction between patients recovered with or without defect. The effect on the working capacity is quite the same.

Thus it may be concluded that it has not by the present investigations been possible to show that the combined treatment is superior to hypertherm treatment, whether clinical, social, or humoral criteria are used as basis of the evaluation, and whether the observation period is on an average 15 months or 4–5 years.

The apparent superiority presented by isolated hypertherm treatment—by use of some of the criteria mentioned above—is hardly real and on close examination appears mainly to be due to minor dissimilarities in the composition of the materials.

It will therefore in what follows be allowable to treat the materials as a whole.

THE EFFECT OF HYPERTHERM TREATMENT AND COMBINED TREATMENT ON THE VARIOUS TYPES OF NEUROSYPHILIS

After the patients have been subjected to the total, very intensive treatment lasting several years, we find the following results, at the statement of which no consideration has been paid to the kind of treatment, the quantity of doses, the gravity of the clinical symptoms, the duration of the neurosyphilitic process, etc.:

General paresis and taboparesis (126): Symptom-free: 24 per cent., symptom-free or improved: 78 per cent. Fit for work: 60 per cent. Restored cerebrospinal fluid: 72 per cent.

Of the neurasthenic, slightly demented patients (56) 32 per cent. are symptom-free. Of the other forms of paresis (70) 17 per cent. are symptom-free. The difference is insignificant ($0.05 < P < 0.10$). The

great difference which *Boas* (1949) found in the frequency of remission in the case of the neurasthenic, slightly demented form of neurosyphilis (83 per cent.) (what *Boas* terms "dementia paralytica incipiens") and the other form (23 per cent.) thus after observation and treatment for a prolonged period proves to be untenable when only the clinical form of the disease is used as basis of the classification. If also the duration of the disease is used as basis of the classification, the relation is considerably different, as will be shown below.

Tabes dorsalis (14): Symptom-free: 29 per cent. Symptom-free or improved: 64 per cent. Restored cerebrospinal fluid: 93 per cent.

Meningovascular neurosyphilis (25): Symptom-free: 60 per cent. Symptom-free and improved: 84 per cent. Restored cerebrospinal fluid: 76 per cent.

Asymptomatic neurosyphilis (10): None of these developed clinical symptoms during the long observation period (2.5–7.5 years). They remained fit for work, but six of them had still a pathological cerebrospinal fluid at the end of the observation period.

The effect of the treatment on special symptoms has not been computed. It should especially be noted that our material includes few patients with atrophy of the optic nerve, for which reason it is unsuitable for an evaluation of the effect upon this symptom.

HYPERTHERM TREATMENT AND COMBINED TREATMENT AS COMPARED WITH OTHER FORMS OF TREATMENT ON NEUROSYPHILIS, ESPECIALLY PENICILLIN TREATMENT

At prognostic investigations of the effect of various therapies upon neurosyphilis it should be kept in mind that the treatment is only *one* of the factors which determine the final issue of the course of the disease. The clinical-social prognosis is a complexly determined resultant of a multitude of different conditions. If these are not quite uniform in the materials compared—or at least can be weighed statistically—a thorough analysis is impossible. *Whelen & Bree* (1954), amongst others, call attention to the intangible factors that are of importance, by pointing out that the prognosis amongst other things depends upon (1) a good pre-illness personality, (2) a dependable and sympathetic prop, and (3) some kind of occupation.

Most prognostically significant factors are, however, considerably easier to ascertain than those mentioned. It should especially be mentioned that although the importance of the duration of the disorder is obvious, this is rarely considered in the literature.

A comparison between the results of various authors is furthermore complicated by the fact that the criteria of cure, fitness, and restoration of the cerebrospinal fluid are difficult or impossible to compare.

It is therefore with extreme caution that we shall try to compare our results with those of other authors. Only investigators who have published fairly large series of examinations, and whose methods and criteria of health approximately correspond to ours will be quoted.

In Denmark *Madsen* (1934 and 1949) and *Lomholt* (1944) have made the malarial treatment the object of thorough discussions. They found complete remission in about 25 per cent., which is in excellent agreement with our results.

Whelen & Bree (1954) found a similar remission percentage. The patients improved during a period up to five years after malarial treatment, but complete remissions did not occur after lapses of two years.

Boas (1949) in 136 patients suffering from paresis found that hypertherm treatment cured 51 per cent. The material, however, mainly consisted of cases of paresis of short duration. Simultaneous penicillin treatment could not be shown to increase the frequency of remission. Some of the patients in *Boas'* material are entered in the present investigations.

Stokes (1945), who published one of the first papers on penicillin treatment of neurosyphilis, found a distinct effect, but it is only from recent years that it has been possible to publish large materials of patients treated with large doses of penicillin.

Dattner et al. (1947) found that 6 million units of penicillin is an optimal dose and by using this obtained a "satisfactory" reaction in 90 per cent. of the cerebrospinal fluids—with an observation period of about 1–2 years. In a later work *Dattner et al.* (1951) have corroborated these findings in a material of 438 cases observed for at least 6 months. It cannot be excluded completely that these results are somewhat better than ours. The criteria of "satisfactory reaction", however, are only humoral: a cell-count of at most 4 per cu.mm and decreasing colloidal gold reaction without relapse during the observation period. However, only 9 per cent. suffered relapse during the observation period, and only 4 patients had an "active cerebrospinal fluid" at the final examination. No clinical evaluation has been communicated.

Callaway et al. (1950), whose clinical criteria agree fairly with ours, have treated 201 patients with penicillin in doses of 4–6 million units and find that a total of 76.8 per cent. have improved clinically or are symptom-free. An increase of the dose of penicillin beyond 4 million units or simultaneous fever therapy cannot be shown to have increased the effect. The total result corresponds closely to ours.

Curtis et al. (1950) in a material of 221 patients treated with penicillin and 209 patients treated with penicillin and malaria found no difference, whether clinically or socially. The humoral results as well were uniform apart from the fact that the combined treatment was somewhat more effective by making Kahn's test negative.

Ingraham jr. et al. (1950) in 603 patients treated with penicillin after an observation period of 5 years found that the cerebrospinal fluid became "normal or near normal" in 55 per cent. of the paretics and 60–70 per cent. of the tabetic patients. Relapse occurred in 5 per cent. of the patients only.

Epstein & Allen (1951) in 81 patients treated with penicillin and artificial fever obtained results quite similar to those of the other authors quoted.

Spiller & Stewart (1950) treated 105 patients with penicillin and 65 patients with penicillin and malaria. They found that about fifty per cent. of the patients improved or became symptom-free—alike in the two groups. Some of the patients, however, were given 2 million units of penicillin only, which must today be considered insufficient. Still, the cerebrospinal fluid improved in 95 and 98 per cent. of the patients, respectively.

Thus it has not been possible to point out any certain difference between the effect of our treatment (hypertherm treatment and combined treatment) and that of penicillin treatment, whether isolated or combined with some other form of fever therapy.

The choice of the right form of treatment of neurosyphilis must therefore depend upon other factors, among which the clinician's temperament cannot be disregarded. He who is responsible must from his subjective basis of evaluation decide how e.g. the risk of rare, but fatal secondary effects should be weighed against the safe experiences of a generation concerning the effectivity of fever therapy. Is it advisable - after less than 10 years' experience of penicillin treatment to abandon the fever therapy knowing it to be capable of stopping the neurosyphilitic process for good? However good the results of penicillin treatment are according to what has been communicated in the literature, demands for further experiences cannot be rejected. A scientific method for the decision of such questions cannot be established, but in order to throw light on the approach to the problem some other relevant facts concerning the treatment of neurosyphilis will be adduced.

THE DURATION OF THE DISORDER AS A PROGNOSTIC FACTOR

Madsen (1934), *Boas* (1949), and *Whelen & Bree* (1954) have emphasized that the chances of a cure decrease strongly with increasing duration of the neurosyphilitic symptoms.

In our material the duration of the neurosyphilitic symptoms could be determined in 142 patients. Of these, however, 3 patients suffered from asymptomatic neurosyphilis, 46 were fit for work, and 18 had a normal cerebrospinal fluid before treatment. If we are to investigate the frequency of remission with different duration of the disorder with clinical, social, and humoral criteria, it will therefore be on the basis of a material consisting of respectively 139 patients with symptoms, 96 disabled, and 124 patients with a pathological cerebrospinal fluid before treatment.

TABLE 2

Duration of disease	Number	Clinical frequency of remission	Social frequency of remission	Humoral frequency of remission
< 1 month	9	78 % (7 out of 9)	63 % (5 out of 8)	78 % (7 out of 9)
1-3 months	13	50 » (6 out of 12)	80 » (8 out of 10)	54 » (7 out of 13)
3-6 »	18	50 » (9 out of 18)	62 » (8 out of 13)	77 » (13 out of 17)
6-12 »	14	43 » (6 out of 14)	86 » (6 out of 7)	67 » (8 out of 12)
1-2 years	28	7 » (2 out of 27)	6 » (1 out of 17)	65 » (15 out of 23)
2-3 »	17	19 » (3 out of 16)	9 » (1 out of 11)	87 » (13 out of 15)
3-4 »	5	20 » (1 out of 5)	40 » (2 out of 5)	80 » (4 out of 5)
4-5 »	7	14 » (1 out of 7)	0 » (0 out of 3)	40 » (2 out of 5)
> 5 »	31	13 » (4 out of 31)	18 » (4 out of 22)	80 » (20 out of 25)
In all	142	28 % (39 out of 139)	36 % (35 out of 96)	72 % (89 out of 124)

The relation between duration of the disorder and frequency of remission (after an observation period of 4–5 years) at different methods of evaluation. In order to facilitate the comparison we have given the figures as percentages, with the absolute figures added in parenthesis. Patients who before treatment were "asymptomatic" when the method of evaluation in question was used, have not been included. See further the text.

As appears from *Table 2*, we found a frequency of remission with these three criteria of respectively 28, 36, and 72 per cent. in the whole material.

With different duration of the disorder we find—*with a clinical and social evaluation—a highly decreasing frequency with an increasing duration of the disorder*. Thus in the case of a duration of up to three months three fourths of the patients are cured as against less than one fifth with a duration of more than five years.

It applies in the case of both criteria that the main change of the prognosis occurs at a duration of the disorder of one year.

At a clinical evaluation it is thus found that there is a frequency of remission of 53 per cent. at a duration of the disorder of less than one year as against 13 per cent. at a duration of more than one year. At a social evaluation the corresponding values are 71 and 13 per cent., respectively. In both cases the difference is very highly significant ($P < 0.001$).

At a still shorter duration of the disorder there seem to be still better results, but the figures are very small. A statistical test may, however, be achieved by means of *Yates'* correction, but whether the distinction is made at a duration of 1, 3, or 6 months, the prognostic difference at a duration of below one year is found to be insignificant ($0.10 < P$). The same is the case if we try to make distinctions at 2, 3, 4, or 5 years.

The decisive prognostic importance which must be ascribed to a duration of the disorder of less than one year is also seen if we investigate this fact within the various groups of disease. For the three main diagnostic groups we thus find the following frequencies of remission:

	Duration < 1 year Percentage	Duration > 1 year Percentage
102 patients suffering from paresis	50 (17 out of 34)	10 (7 out of 68)
17 patients suffering from tabes dorsalis	60 (3 out of 5)	8 (1 out of 12)
19 patients suffering from meningovascular neurosyphilis	54 (7 out of 13)	33 (2 out of 6)

The differences between the results of treatment at varying duration of illness thus is of quite another order of magnitude than the differences appearing by change of other variables, whether diagnostic subgroup, length of the observation period, or (especially) the kind of treatment.

If clinical-social standards of evaluation are used, the duration of the disorder is thus a much more significant prognostic factor than the kind of treatment—provided that one of the effective therapies mentioned is used.

As thus it is necessary to proceed to effective treatment immediately when a case of neurosyphilis is diagnosed, this is *a strong argument for* immediate use of the most easily accessible of these remedies—at present penicillin.

If, however, humoral criteria are used for an evaluation of the effectivity of the treatment, we find quite another relation between duration of the disorder and prognosis.

As appears very clearly from *Table 2, Col. 3, the cerebrospinal fluid is restored in about three fourths of the patients by treatment— regardless of the time during the course of the illness when the treatment of the patient started, and as appears from what precedes regardless of the question whether the patient in this way was cured of the clinical-social syndrome for which he sought treatment and which, indeed, must be the actual object of the treatment.*

This is a strong argument *against* accepting a new form of treatment—in this case penicillin—*on the ground* that it is capable of restoring the cerebrospinal fluid. It is the patient's complaint that is to be cured, not a particular symptom.

The importance of the humoral syndrome for the diagnosing of neurosyphilis is obvious, but as the correlation between the clinical and the humoral findings according to the statement above must be supposed to be low, there may be reason to investigate this relation more closely at various times of the course of the disorder with reference to an evaluation of the importance of the values of the cerebrospinal fluid and their suitability as indicators for retreatment.

THE RELATION OF THE HUMORAL SYNDROME TO THE CLINICAL-SOCIAL STATE

In order to investigate this we have in *Table 3* put the findings of the cerebrospinal fluid in relation to the clinical-social state at the following three different times of examination: before treatment, 15 months and 4–5 years after the first treatment.

A close interrelation between the findings of the cerebrospinal fluid on one hand and the clinical-social state on the other had to appear in two ways:

(1) If the assumption of covariation were correct, then it was to be expected that among the symptom-free patients there were more with a normal cerebrospinal fluid than among the patients showing symptoms. Inversely, we should of course expect more patients with a pathological cerebrospinal fluid among those showing symptoms than among the symptom-free patients. A similar reasoning may be applied to the relation between social and humoral state. Whether this expectation is correct may be investigated by means of the χ^2-method.

(2) If the assumption of covariation were correct, we should furthermore expect that the total number of patients in the case of covariation was significantly larger than the number of patients without covariation, to the effect that the sum of patients having no symptoms as well as a normal cerebrospinal fluid or symptoms as well as a pathological cerebrospinal fluid is greater than the sum of patients who did not show covariation. This figure is therefore given in the last column of *Table 3*.

Before treatment: It is obvious that at this time there is a correlation between the clinical and the humoral state. 94 per cent of the patients with a pathological cerebrospinal fluid also show symptoms, and 88 per cent of the patients having symptoms have a pathological

TABLE 3

Number of patients: 194			Humoral state: Normal	Humoral state: Pathol.	Covariation
Before treatment	Clinical state	Sympt.-free	0	11	83 % (161)
		Showing sympt.	22	161	
	Social state	Fit for work	8	70	57 % (110)
		Disabled	14	102	
About 15 months follow-up	Clinical state	Sympt.-free	37	10	47 % (90)
		Showing sympt.	94	53	
	Social state	Fit for work	83	43	53 % (103)
		Disabled	48	20	
About 4-5 years follow-up	Clinical state	Sympt.-free	44	20	40 % (77)
		Showing sympt.	97	33	
	Social state	Fit for work	91	30	59 % (114)
		Disabled	50	23	

The relation between clinical (resp. social) and humoral state at different times of examination. The numbers of patients who simultaneously show the qualities in question are given in columns 1 and 2. Column 3 shows the number of patients in whom the qualities vary in the same direction. The absolute figures are indicated in parenthesis. See further the text.

cerebrospinal fluid. The χ^2-method cannot be used in the case of this distribution as no symptom-free patients also had a normal cerebrospinal fluid.

Covariation is found in 83 per cent., i.e. that in 83 per cent. of the patients there is good agreement between the clinical findings and the humoral values. In 17 per cent. we found either clinically asymptomatic forms with a pathological cerebrospinal fluid or clinical syndromes in which the cerebrospinal fluid was normal (with our boundaries of normality).

On the other hand we found no connexion between humoral state and working capacity. It is true that e.g. 88 per cent. of those completely or partially disabled have a pathological cerebrospinal fluid, but so has 90 per cent. of those fit for work. The difference is insignifi-

cant ($0.10 < P$). Covariations is found in a total of 57 per cent. of the patients only.

After treatment: Regardless of the question whether the problem is investigated 15 months or 4–5 years after the first series of treatments quite the same conditions are found. Covariation is found in only about 50 per cent. of the patients, and when the distributions is investigated by means of the χ^2-method we find $0.10 < P$. Thus there is no agreement with the hypothesis assumed.

For instance it may be mentioned that after 4–5 years

23	per cent.	of	the	patients	have	a	normal	spinal	fluid and are symptom-free
17	„	„	„	„	„	„	pathol.	„	„ and show symptoms
50	„	„	„	„	„	„	normal	„	„ but show symptoms
10	„	„	„	„	„	„	pathol.	„	„ but are symptom-free

Disregarding the very clear connexion between the clinical and the humoral state before the beginning of the treatment, we thus may conclude that *we have not at any later time succeeded in finding any correlation between clinical symptoms and pathology of the cerebrospinal fluid.*

Epstein & Allen (1951) in a material of 81 patients found a "tendency towards parallel changes", which, however, has not been statistically substantiated. *Curtis & Allen* (1951) found no correlation in their examination of 430 patients, which is in full agreement with our observations.

When *Dattner* (1951) in his works makes the restoration of the cerebrospinal fluid his primary object, this is not in our opinion justifiable. He says, "We are convinced that no attempted summary of the clinical findings would be helpful in evaluating treatment."

Even if *Dattner*'s assertion should be correct, it is not in our opinion possible conversely to conclude that the values of the cerebrospinal fluid should be a more reliable or exact expression of the neurosyphilitic process in the central nervous system than the clinical symptoms.

Special importance is often in the daily clinical routine attached to the examination of the cerebrospinal fluid after the first series of treatments. In order to evaluate the justification of doing so on an empirical basis, we have made the following investigations.

THE HUMORAL STATUS ABOUT 15 MONTHS AFTER THE FIRST SERIES OF TREATMENTS AS A PROGNOSTIC FACTOR AND INDICATOR FOR RETREATMENT

As a suitable material we have selected the group of patients with the following common course: first series of treatments → examination about 15 months after treatment → 4–5 years' observation period during which some patients have been retreated while others have not → examination 4–5 years after first series of treatments.

These conditions were fulfilled by 161 patients.

The material can then be grouped according to the following characteristics:

(a) *Normal* or *pathological* cerebrospinal fluid with follow-up about 15 months after treatment.

(b) *Retreatment* or *no retreatment* between the examinations (respectively 15 months and 4–5 years after treatment).

By crossing these characteristics we get the following four groups of patients:

(1) 61 patients with a normal cerebrospinal fluid. Later retreatment
(2) 44 „ „ „ „ „ „ Later no retreatment.
(3) 52 „ „ „ pathol. „ „ Later retreatment
(4) 4 „ „ „ „ „ „ Later no retreatment

Unfortunately the last group is so small that it must be left out of the investigations, which highly impairs their value.

The other three groups are comparable, i.a. as regards the duration of the neurosyphilitic process and preceding treatment.

The clinical, social, and humoral states of these groups of patients 4–5 years after treatment appear from *Table 4*.

The changes which have taken place as regards the material of patients as a whole appear from the last column.

From a clinical point of view it is most conspicuous that no change takes place in three fourths of the patients. It is true that the number of patients denoted as symptom-free has increased by 17, but at the same time the state of 12 patients has been aggravated, and the number of patients fit for work has been reduced by 5. For the material of patients as a whole the change in a clinical-social respect thus is insignificant. The same applies to the total humoral prognosis.

By comparing the first and the second column we may be informed of the importance of retreatment for the categories of patients with a normal cerebrospinal fluid. It appears that retreatment cannot make a single patient fit for work. In both groups the number of patients

TABLE 4

Number of patients: 157		Normal spinal fluid Retreatment		Normal spinal fluid No retreatment		Pathol. spinal fluid Retreatment		Total	
		Ab. 15 months	4-5 years	Ab. 15 months	4-5 years	Ab. 15 months	4-5 years	Ab. 15 months	4-5 years
Clinical state	Sympt.-free	18	21	10	17	6	13	34	51
	Showing sympt.	43	40[1]	34	27[2]	46	39[3]	123	106[4]
Social state	Fit for work	38	38	33	34	36	30	107	102
	Disabled	23	23	11	10	16	22	50	55
Humoral state	Normal	61	42	44	39	0	29	105	110
	Pathol.	0	19	0	5	52	23	52	47

[1] Improved 3, Unchanged 29, Aggravated 8 [2] Improved 1, Unchanged 26, Aggravated 0 [3] Improved 5, Unchanged 30, Aggravated 4 [4] Improved 9, Unchanged 85, Aggravated 12

The clinical, social, and humoral state of 157 patients is indicated 15 months as well as 4–5 years after the first series of treatments. Their state is set in relation to the question whether they had a normal spinal fluid 15 months after the first series of treatments, or were retreated later, respectively. See further the text.

denoted as symptom-free increases a little, but most in the group which has not been retreated (not significant, however; $0.5 < P$ by *Yates'* correction).

For that matter, it is doubtful whether this uncertain clinical improvement can be attributed to the retreatment. *Whelen & Bree* (1954), *Callaway et al.* (1950) have observed that the improvement after a single series of treatments may continue for several years.

In both groups of patients we find relapse to a pathological cerebrospinal fluid (23 per cent. in all), but with the largest number in the group which has been retreated. The difference is even slightly significant ($0.01 < P < 0.02$), i.e. that retreatment is not particularly effective to restore the cerebrospinal fluid relapse which in many of the cases was the basis of retreatment. Thus it may be concluded that *retreatment in cases in which the cerebrospinal fluid had been restored after the first treatment cannot make the prognosis better apart from what has already been obtained,* and thus we may bear out *Dattner*'s (1951) assertion: "In our experience, significant clinical improvement cannot be effected by treating patients for neurosyphilis when the spinal fluid findings indicate no activity." Furthermore we may by

observation of the third column learn that *in the cases in which the spinal fluid is still pathological no certain clinical-social improvement is obtained by retreatment.* Even though the spinal fluid is restored in more than fifty per cent., the clinical-social changes are doubtful or missing. It is true that the number of those denoted as symptom-free is increased by 7, but at the same time the number of those completely fit for work is reduced by 6.

A comparison between the first and the third column may illustrate how much it means for the prognosis whether the spinal fluid findings after the first series of treatment are normal or not. It is clearly of no importance for the clinical-social prognosis. In the case of the humoral prognosis we see that—in spite of retreatment—19 out of the 61 patients who at the first re-examination had a normal spinal fluid, had got a pathological spinal fluid and that in spite of retreatment 23 out of the 52 patients who had a pathological spinal fluid on the first re-examination, still have this on the last re-examination. The difference is not significant ($0.10 < P$), and so we may *conclude that the cerebrospinal fluid findings —provided that the case has been retreated after the first series of treatments are of no prognostic importance, neither humorally, socially, nor clinically.*

From a comparison between the second and the third column—if there *are* differences— we cannot draw any sure conclusions (as both variables have changed), but the pronounced agreement between the clinical-social results makes it justifiable considering the previous findings to *conclude that the fate of the patients has essentially been decided at the end of the first series of treatments.*

Therefore the early institution of effective therapy is the most important object of any form of treatment. At the evaluation of the result of the treatment it should be considered that all the symptoms which we can observe are very *indirect* expressions of the neurosyphilitic process, and furthermore, that these symptoms are mutually uncorrelated, for which reason we can only judge the result of the treatment by observation of a plurality of them.

SUMMARY

369 patients suffering from neurosyphilis were treated during the years 1943–53, but only 194 patients form part of the present material, as we have made the demand on the material that a psychiatric-neurological examination, an evaluation of the patient's working capacity, and an examination of his cerebrospinal fluid should have been made before as well as at least six months after the treatment.

An account is given of previous treatment, duration of the neurosyphilitic symptoms, and diagnostic grouping. Only about one third of the material offers severe psychopathological symptoms, and only about half of the patients are completely or partly disabled. The result of the treatment has been evaluated clinically as well as socially and humorally, and the asymptomatic patients, those fit for work, and the patients who had a normal cerebrospinal fluid have been deducted in the respective statements. The results have been made up after the first series of treatments (average observation period 15 months) as well as after the intensive treatment lasting for several years (average observation period 4–5 years).

At the first series of treatments 101 patients have been subjected to hypertherm treatment, 73 to combined treatment (hyperthermia simultaneously or alternating with penicillin), and 20 to penicillin.

After the complete treatment 58 have been through hypertherm treatment, 119 combined treatment, and 17 penicillin treatment.

The indication for retreatment has been determined by making a total evaluation of the clinical, social, and humoral aspects of the patients' state. The minimum treatment was 10 hypertherm treatments for at least 30 hours at a body temperature of 40° C. or more, respectively at least 6 million units of penicillin.

The comparison between the results of the treatment has been estimated by means of the χ^2-method.

The investigations allow of a conclusion that the combined treatment cannot be shown to be superior to hypertherm treatment, whether clinical, social, or humoral criteria are used as basis of the evaluation, and whether the observation period is on an average 15 months or 4–5 years. The apparent superiority offered by hypertherm treatment—at the use of some of the criteria mentioned—is hardly real and on close examination appears mainly to be due to minor dissimilarities in the composition of the material.

For the material as a whole we find at an observation period of 15 months: symptom-free 20 per cent., symptom-free or improved 75 per cent. 44 per cent. have become fit for work. The cerebrospinal fluid has been normalized in 65 per cent. At an observation period of 4–5 years we find correspondingly: symptom-free 30 per cent., symptom-free and improved 74 per cent. fit for work 40 per cent. The cerebrospinal fluid was normalized in 70 per cent.

It is shown that the results of the treatment are fairly uniform in the case of the different forms of neurosyphilis and independent of the special clinical picture in which paresis manifests itself.

As the prognosis of neurosyphilis is complexly conditioned and

dependent on other factors than the treatment, a comparison with the results of other authors is difficult and can only be made with authors whose methods and criteria of cure approximately correspond to ours.

We did not succeed in demonstrating any sure difference between the effect of our treatment (hypertherm treatment and combined treatment) and the information in the literature about penicillin treatment, whether isolated or combined with some other form of fever therapy.

At investigations of the duration of the disorder as a prognostic factor, we found at a clinical-social evaluation a very decreasing frequency of remission with increasing duration of the disorder, and it is shown that a duration of the disorder of less than one year is a much more significant prognostic factor than the kind of treatment. On the other hand it can be shown that the cerebrospinal fluid is restored in about three fourths of the patients—regardless of the time within the course of the disease at which the patient is brought under treatment, and of the question whether the patient in this way is cured of his clinical-social syndrome. Therefore, penicillin treatment cannot be accepted on the ground that it is capable of restoring the cerebrospinal fluid, whereas it must be admitted that the dependence of the prognosis on the duration of the neurosyphilitic symptoms speaks highly in favour of immediately using the at present most easily accessible effective remedy of penicillin.

At investigations of the covariation between the humoral and the clinical-social states it is shown that whereas there is a clear covariation before treatment, it is not possible later in the course of the disorder to show any correlation between clinic and cerebrospinal fluid pathology.

It is substantiated that the patients after the improvement which sets in after the first series of treatments, do no improve further, whether the cerebrospinal fluid has been restored or not. The cerebrospinal fluid findings after the first series of treatments are not of any prognostic importance, whether humorally, socially, or clinically. The patients' fate is in the main decided at the end of the first series of treatments. Therefore the early institution of an effective therapy is the principal object of any form of treatment. The observable symptoms are all indirect expressions of the neurosyphilitic process, and as they are mutually uncorrelated, the result of treatment can only be evaluated by observation of a plurality of these.

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THE SENSORY GANGLIA: RECENT ANATOMICAL, PHYSIOLOGICAL AND PATHOLOGICAL CONTRIBUTIONS

By

J. B. Brierley

The spinal sensory ganglia and their cranial counterparts are, with the exception of the autonomic ganglia the sole collections of nerve cells lying outside the central nervous system. They constitute a series of well defined structures possessing anatomical and physiological fatures which set them apart from the peripheral nerves and from the spinal cord. In spite of their great importance as the loci of the cell bodies of the peripheral sensory neurones, their well protected and relatively inaccessible position has been a major factor contributing to the paucity of knowledge concerning their involvement not only in pathology of spinal cord and nerves but also in a wide range of systemic disease.

The purpose of the present communication is to suggest certain correlations between recent information relating to the anatomy, physiology and biochemistry of the sensory ganglia and their pathological modifications in disease.

ANATOMICAL ASPECTS

1. *Blood Supply.*

While the histological appearances of the sensory ganglia are well known, certain anatomical features of their vasculature merit attention in view of the permeability properties to be discussed later.

Bergmann and Alexander (1911) have shown that the ganglionic arteries are derived from the spinal branch of the corresponding segmental artery and enter the ganglionic substance both at its poles and by penetrating the dural sheath.

Within the grey mater of the ganglion the capillary network is very tortuous and almost every ganglion cell is surrounded by its own loop or loops (Bergmann & Alexander, 1941).

The capillary plexus in the new born infant displays occasional bead-like dilatations of diameter two or three times that of the capillary itself. At three to ten years of age these beads are more numerous and are up to five times the capillary diameter, at about thirty years they attain their largest size and "... consist of bead-like or ampullary dilatations of capillary or precapillary channels which reach eight to twenty times the size of the diameter of the vessel in the course of which they occur. Those occurring in the course of capillaries measure 40–100 μ in diameter," (Bergmann & Alexander, 1941).

The dilatations are observed only in the gray substance of the ganglia and often occupy the site of a ganglion cell which has disappeared. The existence of these dilatations must be borne in mind when a comparison (based solely on length) is made between the vascular densities of the root ganglia and other parts of the nervous system. Thus Dunning & Wolff (1937) have expressed capillary densities in the nervous system of the cat as the length of capillary in millimetres per cubic millimetre of tissue and present the following figures:—

Parietal cortex	683–882 mm/c.mm.
Trigeminal ganglion	547 mm/c.mm.
Supr. Cerv. Gang	788 mm/c.mm.

Thus from the above data for the bead-like dilatations and the capillary density, it can be shown that the capillary endothelial area in a cubic millimetre of cortex would be equalled by that in the same volume of ganglion if the beads were to account for only 1.0 % of the total capillary length.

2. *The ganglia and the sub-arachnoid space.*

The special features of the sub-arachnoid cul-de-sac around the emerging nerve roots just proximal to the root ganglion have been investigated by many workers since Quincke (1872) demonstrated the escape of cinnabar particles from this region along lumbar nerves and into cervical lymph nodes. Similarly, Ivanow (1927), using a fine Indian ink suspension introduced into the lumbar sub-arachnoid space of dogs, observed that several days later there was visible ink in deep cervical, posterior thoracic, posterior abdominal and pelvic lymph nodes. A more detailed picture was provided by Ivanow & Romodanow-

sky (1928) who described the dense accumulations of ink in the sub-arachnoid cul-de-sac and noted that there was no spread of the particles over the surface of the ganglia or into the spinal nerve.

Substantial confirmation of the findings of earlier workers was obtained by Brierley & Field (1948) who introduced a fine suspension of Indian ink into the cranial sub-arachnoid space of rabbits under physiological pressure conditions. The outflow of particles into prevertebral lymph nodes was described together with their accumulation ("ink-cuffs") confined to the arachnoid culs-de-sac.

This description has been modified by Brierley (1950) largely as the result of the introduction of larger quantities of dialysed ink by the cisternal route. Forty-eight hours later there was naked eye evidence of the spread of ink over the surface of the root ganglia particularly in those associated with the three main roots of the sciatic nerve. Microscopically it was seen that ink had not only accumulated in the sub-arachnoid cul-de-sac, but had also passed through the arachnoid into the ganglion. Here it moved slowly among the ganglion cells to emerge eventually in the mixed spinal nerve where it could be seen as columns of particles lying betwen individual nerve fibres. Ink had also passed outwards through the arachnoid into the subdural space within which it drifted some way over the ganglion before re-entering its substance to lie among the peripheral ganglion cells.

Further, in spite of this extensive migration of particulate mater, the anatomical reality of the subarachnoid cul-de-sac has been established by histological examination, thus confirming the findings of Somberg (1947). No evidence was found to support the view of Hassin (1947) that the subarachnoid space is in open communication with the tissue spaces of the ganglion and with the perineural space.

It may be concluded that the cul-de-sac of the sub-arachnoid space around the nerve roots is a subsidiary site for the excretion of cerebrospinal fluid which may pass either via segmental lymph channels into prevertebral lymph nodes (Brierley & Field, 1948); (Field & Brierley, 1948), or via the substance of the root ganglion into the spinal nerve. It is emphasised that this outflow is greatest in the lumbosacral region, rather less in the cervical and least in the thoracic part of the spinal cord. As pathogenic organisms may be expected to behave in a manner similar to ink particles once they have gained access to the cerebrospinal fluid, they will accumulate in close relation to the nerve roots, the meninges covering the latter and the root ganglion itself. These facts are of obvious importance in the neuropathology of these several structures and will receive consideration later.

PHYSIOLOGICAL ASPECTS

1. *Impulse Transmission.*

The occurrence of a brief delay in the transmission of an impulse through the root ganglion of the frog was demonstrated by Erlanger, Bishop and Gasser (1926) who were, however, unable to offer a satisfactory explanation of their finding. The delay was shown to be rather less than one hundredth of that involved in transmission at the spinal synapse and was thought to take place at the point of junction of the central and peripheral ganglionic processes. If conduction was of a to-and-fro nature along the stem process, the latter would be expected to display the usual refractory period which would be about ten times the observed delay. If, on the other hand, the stem process did not become refractory, to-and-fro conduction would occur within a time less than half that experimentally recorded.

Von Brücke et al. (1941) demonstrated a delayed recovery in responsiveness in sensory compared with motor fibres of the bull-frog and attributed this delay to the ganglion cell. Recently Dun (1951) has confirmed the value obtained by Erlanger, Bishop and Gasser for the relatively refractory period which he too believes to occur at the point of bifurcation of the stem process.

No worker has, as yet, been able to demonstrate a role for the cell body in impulse conduction. However, the possibility of such a role exists and with it, the possibility that the metabolic state of the cell as well as circulating substances (including drugs) may affect the emerging impulse stream in the dorsal nerve roots.

2. *Vascular permeability in the sensory ganglia.*

(a) *Vital Dyes.*

The staining of the autonomic and sensory ganglia by intravenously injected vital dyes, the central nervous tissue remaining unstained, was demonstrated by Behnsen (1927), Doinikow (1931) and in detail by Tschetschujewa (1930). The later using trypan blue in rabbits recorded that both group of ganglia exhibited naked-eye staining after 48 hours. In the spinal ganglia the granules of dye appeared largely in mesodermal cells and as finer granules in the satellite cells. In the neurones themselves only a fine blue stippling was to be seen. These results would imply either the absence of the "blood brain barrier" to acid dyes or the presence in ganglion cells of an "affinity" for dye as suggested by King (1938).

It should be noted that in young animals there is fairly uniform

visible staining of the nervous system whereas in the mature animal central nervous structures in general have lost this staining ability (except the pineal, tuber cinereum and the area postrema) and only the sensory and autonomic ganglia and to a lesser extent peripheral nerve retain this property.

The availability of radioactively labelled vital dyes has made it possible to investigate quantitatively the distribution of such dyes in the central and peripheral nervous systems of adult and immature animals. Brierley (1953) has shown that the acid dye Erythrosin, labelled with radioactive iodine (I^{131}) when injected intravenously into immature rabbits attains root ganglion concentrations 3.1 times those in the central nervous system (average) after 10 minutes. With longer survival periods the ganglion C.N.S. ratio rises to 3.8. In adult animals the concentration of dye in the central nervous system is less than half that in the immature animal even after one hour. The root ganglia dye concentration during the first 15 minutes lies within the range of central nervous samples and rises only slowly thereafter to attain a peak betwen one and two hours when the ganglion/C.N.S. ratio is 4.1.

In similar experiments carried out with iodine ^{131} –labelled fluorescein (diiodofluorescein) the ganglion/C.N.S. ratio of the immature group is 5.8 at 5 minutes rising to 11.7 at one hour while in adults the ganglion/C.N.S. ratio is only 2.1 at 5 minutes and rises to 11.5 at one hour.

Thus both these acid vital dyes when injected into adult animals produce ganglion C.N.S. ratios that rise steadily with survival time. At the same time the actual concentration of dye in the central nervous system is in fact falling while that in the root ganglia is rising. In the immature animals the ganglion C.N.S. ratios remained steady or rose only slightly while the actual dye concentrations decreased in each type of tissue. Further, for each dye the ganglion activities are higher in the immature animal than in the adult and this difference (at 15 minutes) expressed as the ratio young/adult is 4.3 for erythrosin and 2.0 for diiodofluorescein. Thus the root ganglia conform to the general rule that immature nerve tissue takes up more vital dye than adult, or perhaps that the vessels in immature nerve tissue are more permeable than in the adult.

(b) *Ions.*

The delayed entry of sodium and phosphate ions into rat and rabbit brain has been demonstrated for the corresponding radioactive isotopes by Manery and Bale (1941) and for chloride by Manery and Haege (1941). The dissimilar rates of penetration into root ganglia and central

nervous tissue of radioactivie phosphate and sodium have been described by Brierley (1952a, 1952b). For phosphate the ganglion brain concentration ratio has been shown to be about 21.0 ten minutes after its intravenous injection, while for sodium thirty minutes after injection the ratio is 6.0. Peripheral nerve occupies a position intermediate between ganglion and central nervous tissue in that the nerve/brain ratio is 11.0 for phosphate and 3.5 for sodium.

The penetrations of ions into root ganglia can be influenced by such procedures as section and faradic stimulation of the sciatic nerve (Brierley 1951). Thus aseptic section of the nerve 48 hours previously results in an increase of 9–104 % in the entry of phosphate into the anatomically related root ganglia. Similarly, faradic stimulation of the nerve produces an increase of 11–53 % in phosphate entry and of 6–54 % in the entry of sodium. These results can be interpreted as demonstrating an increased capillary permeability to the ions in question or a local vasodilatation (with increased blood flow) or both. For sodium, the relation of this increased penetration into intact nerve, to the "sodium pump" of Hodgkin and Katz (1949) has yet to be decided.

(c) *Drugs.*

The entry of drugs into the sensory ganglia has been investigated by Brierley (1952c) who briefly examined the distribution in the rat nervous system of sulphanilamide iodinated with I^{131} and found that the highest neural concentrations were reached in the root ganglia. Thus the ganglion/brain ratio 15 minutes after injection was 1.5–1.7: 1 and the ganglion nerve ratio 1.1–1.5: 1.

The anti-malarial drug paludrine is known to enter the central nervous system to a very limited extent (Spinks, 1947) but I^{131} iodinated paludrine, after intravenous injection into rats, reaches its highest neural concentration in the root ganglia to give ganglion/brain ratios at 15 minutes of 5.0–5.3 and ganglion/nerve ratios of 4.1–7.5; Brierley (unpublished results).

In view of the unusual vascular permeability in the senisory ganglia it appeared reasonable to include these structures in any quantitative study of the distribution of an analgesic in the nervous system. Thus Brierley & McCoubrey (1953) have compared the tissue distribution of an analgesic (p. cyclohexyloxy-α-phenylethylamine) with a chemically related but non-analgesic substance (p. isopropyloxy-α-phenylethylamine) and have demonstrated that there is no marked difference in their tissue distributions 20 minutes after intraperitoneal injection. After intravenous injection the concentrations of the analgesic in rat

and rabbt root ganglia were respectively just over and just under half that of the cerebral cortex. In the monkey the corresponding fraction was about one third. It was further estimated that ganglion cells accounted for only 35–47 % of the area of Nissl stained sections of root ganglia so that a corresponding correction for drug concentration would being the latter up to at least that of cortex. The concentrations of drug in peripheral nerve and central white matter were found to be insignificant so that attention must be focussed on the aggregations of grey matter within the pain pathway and of these the sensory ganglia will be the first encountered by the incoming pain impulses. Further conclusions are clearly unjustified at present but it would seem that electrophysiological techniques are most suited to decide the level at which the sensory inflow is attenuated.

3. *Biochemistry and Histochemistry.*

The available literature provides only two investigations of the oxygen consumption of sensory ganglia, firstly that of Holmes (1932) who investigated the respiration of chopped sheep trigeminal ganglia three hours after death. The respiration of the ganglion was remarkably low, being only about one eleventh that of sheep cerebral cortex and only a little greater than that of the nerve itself.

The influence of the mode of tissue preparation upon its respiration was shown by Dixon and Meyer (1936) who "found that even the slight injury to the ganglion resulting from chopping with scissors caused the respiration rate in glucose to fall rapidly to one half of its initial value in 2 hours."

A recent investigation by McIllwain (1952) in rabbit lumbo-sacral root ganglia not only confirms the advantages of sliced tissue but demonstrates that the respiration rate is about a third that of the cerebral cortex. The ganglia were cut longitudinally into strips (0.3 mm thick) with a sharp scalpel, incubated in glucose saline and their respiration measured over periods up to 3 hours. During this time little change was to be noted in the rate provided the experimental conditions were kept constant.

Initial rates of respiration (on wet weight basis) with 13 mm glucose in saline averaged 403 $mm.^3$ g./hr. and final rates 470 $mm.^3$ g. hr. For rabbit cerebral cortex in glucose, respiration rates were 1232–1456 $mm.^3$/g./hr. It is interesting to note that the respiration rate of ganglia could be increased at least 60 % by the application of electrical pulses under conditions (McIllwain, 1951) which cause a similar or greater increase in the respiration of cerebral tissue.

The above figures for ganglion oxygen consumption are for tissue prepared by dividing the nerve fibres as close as possible to the poles of the ganglion and by removing the ventral root. Nevertheless the samples examined inevitably include the connective tissue elements of the capsule as well as nerve fibres. The respiration of both of these is low and probably contributes little to the figures obtained. Therefore, it may be concluded that the respiration of the structural unit, ganglion cell plus satellites, is probably greater than the values stated above. If, in fact, the available figure for the nerve fibre content of the root ganglia (Brierley & McCoubrey, 1953) is used to correct the resting respiration rates, these become 1142 and 1342 $mm.^3$ gm. hr. The relative contributions of the ganglion cells and satellites to these values cannot, as yet, be decided.

It can be seen, then, that the values for both respiration and vascularity, when corrected as above, are closely similar to those of cortex. An important difference lies in the fact that the sensory ganglia (devoid of synapses) are not subject to stimulation from other parts of the nervous system. If it is permissible to correlate the vascularity and respiration of the cortex with the richness of cortical and subcortical influences mediated through synapses, then the similar vascularity and respiratory rate of the sensory ganglia may be related to the constantly changing environmental stimulation mediated through the peripheral receptors.

PATHOLOGICAL ASPECTS

1. *Contralateral ganglion changes.*

Considerable interest attaches to the neglected investigation of Nittono (1923) into the bilateral effects during a period of 90 days of the unilateral section of branches of the trigeminal nerve in the albino rat. The branch divided was either the infraorbital or the mental nerve and in every animal the trigeminal ganglion and nerve trunk of both sides were examined.

The ipsilateral ganglion cells exhibited various degrees of chromatolysis leading to the loss of some cells and the recovery of others. Congestion of the blood vessels was noted on the first day and slight extravasations of blood on the second, the normal vascular picture being restored by about the 14th day. In the mesodermal tissue of the ganglion there was swelling of nuclei and cells and the appearance of "looseness" of connective tissue reaching a maximum on the 5th to 7th day. It was remarkable that similar but less intense changes were to be seen in the contralateral ganglion.

Nittono recalls the changes observed in the contralateral nerve and ganglion after unilateral section of the rabbit vagus nerve by Koster (1903) and suggests as a mechanism to explain the contralateral effects, either a general nutritional response to the operative interference, a disturbance of the blood supply finding a bilateral expression or an intoxication due to the diffusion of substances formed on the operated side.

2. *Virus Diseases.*

Pathological changes in the sensory ganglia have been frequently reported in a variety of virus diseases including rabies, poliomyelitis, herpes febrilis and herpes zoster. In each disease a consideration of the ganglionic lesions may throw some light upon the postulated routes of entry of virus into the nervous system and upon the related problem of the mechanism by which such peripheral events as trauma or infection may determine the initial site of central nervous involvement.

The peripheral nerve as a pathway of virus to the central nervous system was first suggested in rabies by Di Vestea & Zagari (1887) as a result of experiments in which rabies virus was injected into the sciatic and median nerves of dogs and rabbits with the production of the typical infection.

In addition to cell degeneration in the spinal cord in rabies, Marinesco & Draganesco (1932) have reported histological changes in nerves and spinal ganglia corresponding to the bitten limb. Characteristically the ganglion presents the Van Gehuchten and Nelis lesion consisting of a more or less degenerate neurone surrounded by round cells. There is in addition a marked leucocytic infiltration, both diffuse and perivascular.

The relative infrequency with which rabies virus has been identified in the blood stream together with the observed relationship between inoculation site and the central nervous lesion have been interpreted as militating against a major role for the blood in the pathogenesis of this disease. Nevertheless it is known that intravenous injection of the virus produces paralytic rabies (Pasteur et al. 1882) and that rabies infection may occur in the offspring of experimentally inoculated female animals (Konradi, 1905–16), strongly suggesting the invasion of the nervous system from the blood.

In poliomyelitis, Flexner, Clark and Amoss (1914) demonstrated the presence of the Virus in human intervertebral ganglia during the preparalytic stage of the disease, that is at a time when excretion of virus from the central nervous system could not have occurred as it is believed to do at a later stage of the disease (Bodian and Howe, 1947).

Recent experimental studies by Faber and his associates have provided considerable evidence of the accumulation of virus in peripheral ganglia, both sensory and autonomic, after inhalation of atomized virus (Faber et al., 1943) and after casual exposure to infected animals (Faber et al. 1950). The later group are of particular interest in that the conditions of normal human infection are more closely parallelled. In three animals deliberately kept in close proximity to infected animals there were lesions in Gasserian, nodose and superior cervical ganglia. Unfortunately the spinal ganglia were not examined in this series.

The conclusion drawn from these observations was that the peripheral ganglia were involved by a centripetal movement of virus and that a similar process may occur in the human disease. Invasion of the central nervous system was thought to be secondary to that of the peripheral system. In the latter the invasive process could be arrested at the level of the root ganglia. The oropharyngeal mucosa was believed to be the portal of entry whence virus was conveyed by peripheral nerves to the related ganglia.

As in rabies, the blood stream had, until recently, been regarded by most workers as unimportant in the dissemination of poliomyelitis virus. However, certain experimental evidence has pointed clearly to the existence of a viraemia in the interval between inoculation and the invasion of the central nervous system. Of particular interest are the elegant experiments of German and Trask (1938) who, in the monkey, inoculated virus into a limb connected to the body solely by the blood vessels. The subsequent invasion by virus of the spinal cord unequivocally implicated the bloodstream as the route of spread of the virus. Brierley & Field (1949) referring to these experiments suggested that "... modifications in the blood brain barrier may permit circulating virus to invade the central nervous system and indicate that spread by the blood is a problem that even now merits further inquiry."

More recently, Horstman (1952) has reported a viraemia in seven out of ten cynomolgous monkeys and in three out of four chimpanzees inoculated by the oropharyngeal route. In all the animals showing a viraemia, virus was present in the blood three to seven days before the appearance of symptoms. Similarly a viraemia in the preparalytic stage of the human disease has been described by Horstman & McCollum (1953).

Bodian (1952) in a review of the pathogenesis of poliomyelitis has emphasised the importance of viraemia and has largely rejected the earlier hypothesis of neural transport. Bodian now considers that "the possible effects of seasonal factors, of physical activity, of pregnancy,

of trauma or of concurrent infections with other agents on vascular permeability become the logical objects of suspicion and curiosity." A relationship between these various factors and vascular permeability would be sought, first of all, within the grey matter of the nervous system, including the sensory ganglia, and most probably as a concomitant of the increased blood flow which results from afferent stimulation.

There is also evidence to suggest that the effect of peripheral influences can be seen in metabolic as well as in vascular changes. Thus the important investigations of Hyden (1943) have shown that stimulation of a sensory or motor cell causes a decrease in the cellular proteins and nucleotides. Further, during the recovery period there is an hypertrophy of the nucleolus associated with an accumulation of proteins and nucleotides around the nuclear membrane as well as in relation to the cell membrane itself (Bodian 1947). As viruses are now held to be self-reproducing systems containing nucleic acid and protein groups and capable of parasitic existence within the nucleoprotein-forming mechanism of the host cell it is pertinent to consider whether the above modifications in protein metabolism may in fact influence the entry or parasitism of a neurotropic virus.

It appears probable then that the vascular and the metabolic consequences within the nervous system of trauma, physical activity, etc. are inseparable and constitute an integrated response to functional activity which may play an important part in the localisation of a neurotropic virus in the related parts of the central nervous system. Such a view must ascribe to the blood stream an important though not necessarily a unique role in the transport of virus to nervous structures, of which the sensory ganglia merit particular attention in that their vasculature lacks the properties of the typical "blood-brain barrier."

3. *Tabes dorsalis.*

Although the pathological picture of tabes dorsalis is well known, no coherent theory of its pathogenesis has yet received universal acceptance and current views are unable to explain adequately the predilection of the disease for the lumbo-sacral region of the cord and for posterior rather than anterior nerve roots.

The pathological process in tabes is not confined to the spinal cord and posterior roots but involves also meninges, sensory ganglia and peripheral nerves. The changes in the posterior columns are believed to be a reflection of the primary involvement of exogenous fibres entering via the posterior nerve roots and are recognisable as a combination of demyelination, gliosis and mild syphilitic vascular disease.

The nerve roots and their related meninges constitute the region of greatest pathological interest and are the focal point of the modern views on the pathogenesis of tabes. The whole nerve root from ganglion to posterior horn of spinal grey matter shows a variable degree of demyelination together with cellular infiltration and vascular damage. The root ganglia may appear normal in the presence of posterior column changes or may exhibit alterations very variable in type and intensity. All stages of cell damage up to complete destruction may be seen, while the satellite cells proliferate and appear to invade the peripheral cytoplasm of damaged ganglion cells. The capsule of the root ganglion is thickened, infiltrated and hyperplastic.

In the pathogenesis of the disease, two parts of the posterior nerve roots have been regarded as particularly vulnerable: (a) The Obersteiner-Redlich zone where the roots penetrate the spinal pia and at the same point lose their neurilemmal sheath. Here syphilitic meningitis is likely to cause nerve fibre degeneration (Obersteiner & Redlich, 1894) or syphilitic toxins moving in the interstitial spaces of the nerve may find a region vulnerable to attack (Orr & Rows, 1914). (b) The nerve root cul-de-sac. An infiltrative lesion of the nerve roots in the cul-de-sac was regarded by Nageotte (1903) as the starting point of tabes. Courville (1945) no longer believes this disease to be a form of parenchymatous syphilis but rather a peri-radicular syphilitic meningitis arising in the cul-de-sac and similar in origin to the process responsible for syphilitic optic atrophy in which optic nerve degeneration is secondary to a lepto-meningitis in the perineural sheath.

A possible relationship between the syphilitic infiltration in the cul-de-sac and the accumulation of particulate matter in this region has been advanced by Brierley (1950). If spirochaetes gain access to the cerebrospinal fluid they may be expected to accumulate in the cul-de-sac and initiate a local meningitis which involves the "nerf radiculaire" and the adjacent root ganglion and its coverings. Such a process would explain not only the involvement of posterior rather than anterior nerve roots, but also the localisation of the disease in the lumbo-sacral region where the culs-de-sac are largest and the C.S.F. outflow most important.

An interesting observation relevant to the possible pathogenesis of tabetic lightning pains has been put forward by Caveness et al. (1949). A 55-year-old male with a 30-year history of syphilis presented no indication of central nervous system involvement other than lightning pains in the lower limbs. Exposure of the left fifth lumbar root ganglion followed by its electrical stimulation gave rise to the typical lightning pains while similar stimulation of two upper thoracic ganglia

produced a sensation "like an electric current". Histological examination of the excised lumbar ganglion showed extensive cell loss, abnormal cell forms and amphycytic proliferation.

Penfield in subsequent discussion advanced the idea that these abnormal ganglion cells gave rise to bursts of discharge equivalent to those from a cortical focus in epilepsy, from the vestibular ganglion in Meniere's disease or from the fifth nerve ganglion in trigeminal neuralgia.

4. *The Deficiency Neuropathies.*

(a) *The Vitamin B complex.*

It is well known that the salient biochemical feature of thiamine deficiency is a pyruvaemia and that while the effects of thiamine lack remain at the biochemical level, administration of the vitamin is promptly curative but after prolonged deprivation, morphological changes take place which thiamine therapy is powerless to reverse.

The final pathological picture of long standing thiamine lack may include one or both of two components. One is polyneuritis no different from that seen in starvation, pellagra and heavy metal intoxications, and in whose development the lack of dietary factors other than thiamine cannot as yet be excluded. The other component may be Wernicke's encephalopathy consisting of the typical pattern of largely symmetrical vascular proliferation and haemorrhages in the grey matter around the aqueduct and third ventricle.

In view of the possible multiplication of aetiological factors contributing to the clinical picture of thiamine lack, those symptoms arising during the period of the reversible biochemical lesion are of particular interest in that they may indicate those neural sites where the biochemical and functional consequences of deficiency first become apparent. The predominance of sensory symptoms at this stage (Joliffe et al., 1939) suggests that the sensory neurones, either in part or in whole are particularly susceptible to thiamine lack.

Degenerative changes in the sensory neurones commence in their distal portions suggesting that these may be directly susceptible to the effects of the abnormal metabolism. Alternatively, these effects may act, in the first instance, upon the cell body, in which case the distal fibre degeneration may be the earliest evidence of deranged function of the cell.

Degenerative changes in the cells of the sensory ganglia of the lumbar rather than other regions of the cord was described in swine by Wintrobe et al. (1938). The animals were fed a diet of protein, carbo-

hydrate and fat together with ascorbic acid, cod liver oil and yeast. The salient clinical feature was ataxia while histologically the root ganglion cells showed considerable pathological change. Numerous residual nodules were evidence of ganglion cell destruction while many surviving cells were shrunken and their capsule cells proliferated. The dorsal nerve roots, the posterior columns of the spinal cord and the peripheral nerves also presented varying degrees of degeneration. These pathological changes were ascribed to a deficiency of either pyridoxine or pantothenic acid. Later Follis and Wintrobe (1945) showed that deficiency of pantothenic acid produced the greater degree of ganglion cell degeneration.

It is to be recalled that pantothenic acid is a constituent of coenzyme A and is therefore involved in processes of acetylation such as the acetylation of choline by choline acetylase or the transfer of the acetyl of pyruvic acid to oxaloacetic acid whereby the former is enabled to enter the citric acid cycle. It is thus apparent that deficiency of pantothenic acid may interfere with the respiration of the sensory neurone although the reasons for the special vulnerability of these structures have yet to be elucidated.

A clinical picture closely resembling that of pantothenate deficiency in swine has been described by Denny Brown (1948) in two cases of bronchogenic carcinoma which presented a combination of sensory loss and progressive ataxia. The outstanding pathological feature was a severe cell loss in the dorsal root ganglia indicated by large numbers of residual nodules. The process was one of primary atrophy without inflammatory or vascular reaction, resulting in destruction of the cell bodies and in degeneration of both their central and peripheral processes. The suggestion was put forward that bronchogenic carcinoma produces a substance that interferes with the normal metabolic role of pantothenic acid, such interference presumably being operative or manifest only in the sensory neurones.

(b) *Vitamin A.*

The mechanism underlying the neurological manifestations of Vitamin A deficiency is still a matter of dispute. According to Wolbach and Bessey (1941) the degenerative changes in the peripheral and central nervous system are the consequence of disordered growth of the vertebral column resulting in pressure on the spinal nerves. Recently, however, Rigdon (1952) has put forward convincing evidence to support the alternative view that neurological lesions can occur in Vitamin A deficiency without skeletal abnormalities. This investigation was

carried out in young ducks maintained on a diet lacking only Vitamin A for up to 10 weeks. At autopsy no overgrowth of bone was observed and there was no evidence of nerve or cord compression. Within the spinal cord, nerve cells were frequently shrunken and dark staining particularly in the anterior horns. The illustrations show more dramatic changes in the dorsal root ganglia where a high proportion of cells are pyknotic and atrophic but the empty spaces to which attention is drawn are more likely to be artefact than evidence of true cell loss. An earlier group of deficient ducks revealed conspicuous haemorrhages in the nervous system as well as foci of cartilage and bone formation.

The reason for the absence of such changes in the series reported on is not known.

5. *Metabolic Disorders.*

(a) *Diabetes.*

Diabetes is perhaps the most important example of a metabolic disorder for whose neurological complications no adequate explanation is as yet forthcoming. Neither hyperglycaemia or ketosis can be held responsible for these complications, which, largely sensory in type, usually involve the lower limbs, often commencing as an aching or gnawing pain. Later muscle tenderness and cramps appear together with a variety of paresthesiae and often a diminution in vibration sense and abolition of tendon reflexes, although ataxia (pseudo-tabes diabetica) is rare.

Virtually the only pathological description of the sensory ganglia is due to Denny Brown (1951) who has pointed out that some diabetics may develop a progressive degeneration of the root ganglia particularly of the fifth lumbar roots, with shooting pains and trophic ulceration of the feet.

While the pathogenesis of diabetic neuritis remains ill-defined, little attention appears to have been given to the effect of insulin lack on the metabolism of peripheral rather than central nervous tissues. It is now considered that the fundamental task of insulin is to overcome the inhibitory action of anterior pituitary hormone(assisted by adrenal cortical hormone) upon the initial phosphorylation of glucose in non-neural tissues, thereby permitting its entry into metabolic processes (Himwich, 1951, p. 82). In the brain, in the absence of insulin, carbohydrate metabolism is unaffected and the respiratory quotient is maintained at unity (Himwich & Nahum, 1932). The independence of brain metabolism from insulin and anterior pituitary influence has been attributed to the inability of the latter to penetrate

the blood brain barrier (Himwich, 1951, p. 80). It is pertinent to consider whether peripheral nerves and ganglia share this immunity from hormonal action and whether the absence of the blood brain barrier in the root ganglia to a variety of substances (vide supra) might also apply to the anterior pituitary hormone. If this were so, the metabolism of the ganglia would be in line with that of non-nervous tissues and be characterised by some degree of inability to utilise glucose. The predominantly sensory symptoms of diabetic neuropathy might then be regarded as the manifestation of such a metabolic disturbance. That the autonomic ganglia may also be involved in diabetes is suggested by the recent review of Martin (1953) who has drawn attention to such disorders as achlorhydria, delayed gastric emptying, impotence, naso- and sudomotor dysfunction and disturbed micturition.

(b) *Amyloid disease.*

The central nervous system in amyloidosis commonly escapes the deposition characteristic of the pathological picture in kidney, liver and spleen. There are, however, several reported instances of the occurrence of amyloid in the peripheral neurones. De Nevasquez and Treble (1938) described chronic peripheral neuritis in a man suffering from diarrhoea for two years. Typical amyloid deposits were seen in the peripheral nerves and in the dorsal root ganglia. This pathological material together with that from two personally investigated cases was described by Denny Brown (1951). In all three the amyloid appeared to have been laid down around blood vessels either as small nodules or in the form of cuffs. Similar appearances in the blood vessels of the peripheral nerves of a case of primary amyloidosis were described by Strich and Wade (1953) although here the root ganglia were not investigated.

Amyloid is a complex substance whose composition still eludes precise chemical analysis. It is known to contain a protein fraction and a sulphate-bearing polysaccharide (Hass et al., 1943). Opinion now inclines to the view that the protein is probably not conjugated with chondroitin sulphuric acid but that this latter substance occurs separately in the surrounding tissue. Letterer (1949) by feeding casein to mice demonstrated changes in the proportions and total quantities of α and β globulins in the plasma and concluded that the globulin fraction of amyloid is derived from an abnormal plasma globulin. Presumably the molecular size of this protein is such as to permit its passage through the vascular endothelium in tissues outside the central nervous system so that its occurrence in root ganglia and to a

lesser extent in peripheral nerve reflects a local permeability to this protein similar to that in the typical visceral sites of accumulation.

(c) *Triorthocresyl phosphate neuropathy.*

The multiple neuritis that occurs both clinically and in the experimental animal as a consequence of the ingestion of triorthocresyl phosphate (TOCP) has now been related to the inhibitory effect of this compound on pseudo-cholinesterase. Earl and Thompson (1952) have shown that in rat, rabbit, chick and man, it is the pseudo rather than the true cholinesterase activity which is reduced by TOCP although there are species differences in the degree of such an inhibition.

The high concentration of the pseudo-cholinesterase in white matter previously demonstrated by Ord and Thompson (1950) was thought to suggest its involvement in myelin metabolism. Inhibition of the enzyme might then be the biochemical basis of the neuropathy, which is largely an involvement of the motor nerves as indicated by the development of flaccid paralysis.

The neuropathological report of Smith and Lillie (1931) describes myelin degeneration in the peripheral nerves and spinal cord but provides no data as to the histological appearances of the dorsal nerve roots or sensory ganglia. The histochemical studies of Koelle (1950) have demonstrated the presence of pseudocholinesterase around the nucleus in the majority of sensory ganglion cells as well as in their satellite cells. These findings confirmed the observations of Sawyer & Hollinshead (1945) who noted the predominance of pseudo- over true cholinesterase in these structures. The virtual absence of sensory symptoms in TOCP intoxication suggests that, in some way, the sensory neurones are protected from the action of TOCP, either because their pseudocholinesterase is insensitive to the chemical or because the latter fails to penetrate the cell.

The recent report of Todrick (1952) is of interest in that true or acetylcholinesterase was shown to predominate in the trigeminal and sympathetic ganglia of the horse. This finding, if confirmed, demands an explanation of the role of the true esterase in the trigeminal ganglion where no synaptic transmission is involved.

6. *Sensory radicular neuropathy.*

(a) *Hereditary.*

The essential pathology underlying this interesting condition has been shown by Denny Brown (1951) to consist of a degeneration of the

dorsal root ganglia, particularly in the lumbo-sacral and to a lesser extent in the eighth cervical and first thoracic ganglia. In addition to a conspicuous loss of ganglion cells and replacement by glial nodules, sections showed hyaline masses giving a weak staining reaction for amyloid and apparently originating around a central core of capillary endothelium.

Clinically these cases frequently present painless ulcers of the feet, shooting pains in the lower limbs and loss of thermal sensation. In contrast to the sensory disorder, atrophy and weakness of muscle were not demonstrable and while upper limb co-ordination was good, the movements of the lower limb were unsteady and irregular. Denny Brown has indicated that the symptomatology may be accounted for by the lesions in the root ganglia without implication of the gray matter of the spinal cord.

A possible connexion between this type of hereditary neuropathy and peroneal muscular atrophy was suggested by the observation that occasionally in the latter condition a peripheral sensory disorder of radicular type has been reported (Marinesco, 1894). In these cases the dorsal nerve roots and posterior columns of the cord present changes which closely resemble those in the hereditary neuropathy.

England and Denny Brown (1952) have examined eighteen of the fifty-seven affected members of a large family in which the dominant inherited trait of peroneal muscular atrophy could be directly traced through seven generations. Two members of this family presented extensive sensory and trophic changes typical of a peripheral neuropathy. No pathological material was available, but changes in the root ganglia, peripheral nerves and posterior roots are rendered probable by the autopsy report of Virchow (1855) in which degeneration of these structures was described in a case of peroneal muscular atrophy. England and Denny Brown consider that peroneal muscular atrophy with greater or lesser degrees of sensory involvement and with or without muscle fasciculation, together with hereditary sensory neuropathy, should all be grouped as radicular neuropathies, thus implying a peripheral or extraspinal primary pathology. Degeneration of the root ganglia must then be regarded as a likely basis for the sensory symptomatology.

(b) *Non-hereditary.*

This group includes those instances or root ganglion degeneration associated with bronchogenic carcinoma described by Denny Brown (vide supra) as well as the three cases reported by McAlpine and Page (1951) in which degeneration of the ganglia was inferred from the

clinical evidence. In two of these latter cases there was sensory ataxia with diminished sensation in the extremities and minimal involvement of the motor system. The third case was one of primary syphilitic posterior ganglionitis.

Although the pathogenesis of the first two cases was obscure, an infective origin was suggested in view of the raised cerebrospinal fluid protein thus relating them etiologically to the more common polyradiculitis of mixed motor and sensory symptomatology (including the Guillain Barré syndrome).

The eight fatal cases of polyganglionitis described by Laurelle & Reumont (1949) were ascribed to some toxic or metabolic agent rather than a virus although two showed an albumino-cytologic dissociation in the cerebrospinal fluid. Histological changes were seen in cranial nerve motor nuclei and in peripheral nerves but were most marked in the sensory ganglia. The latter were swollen as a result of a primary proliferative and hyperplastic process resulting in ganglion cell degeneration.

DISCUSSION

The foregoing selective review has demonstrated that a variety of anatomical and physiological features characterise the sensory ganglia as unique collections of synapse-free nerve cells, satellite cells and connective tissue elements lying outside the central nervous system. The solution of many of the problems connected with these structures may well be assisted by reference to their phylogenetic history which is essentially that of a migration away from the axial nervous system. Thus in Amphioxus there are no true spinal ganglia, the sensory nerve fibres arising from ganglion cells in the dorsal region of the spinal cord. There are, however, a few ganglion cells among the peripheral nerve fibres which may be regarded as the fore-runners of the extra-spinal ganglia of the true vertebrates. The sensory ganglia of the Cyclostome lie close to the spinal cord which still contains groups of ganglion cells in their original dorsal position.

With the formation of discrete extra-medullary ganglia there was also a gradual transition from the bipolar to the unipolar cell type, although even in man a small proportion of spinal ganglion and all acoustic ganglion cells still retain their bipolar form.

An important consequence of ganglion migration has been the development of an independent and characteristic vascular supply distinguished in particular by the unusual permeability properties described above. The explanation of the latter must surely be sought in the

metabolism of the ganglion cells when studied in relation to the function performed by them. It is here that precise information is required as to the part played by the cell bodies in the transmission of the sensory impulse to the spinal cord. That the cell body is probably not unimportant in this connexion is suggested by the changes in nucleoprotein metabolism (Hyden, vide supra) and the increased penetration of ions (Brierley, vide supra) consequent upon stimulation of the peripheral nerve. In both these instances the relationship between the demonstrable metabolic change and the functional state of the ganglion in terms of impulse transmission remains to be established.

It is perhaps worth emphasising that the very anatomical isolation of the sensory ganglia renders them particularly accessible to combined functional, metabolic and structural investigations. The electrophysiological technique, readily applicable in the intact animal to action potential recording from central and peripheral ganglionic processes, affords a useful method of assessing the functional state of the sensory neurones. Information thus obtained would be of considerable use in evaluating the effects of, for example, anoxic states, cholinesterase and thiamine inhibitors, depressant and excitatory drugs, respiratory poisons and hormones.

The various clinical and experimental facts also presented above underline the involvement of the sensory ganglia in such diverse conditions as virus disease, vitamin deficiencies and metabolic disorders. Attempts to explain such involvement again may reveal the many aspects of the physiology of these structures in which our knowledge is either limited or even wholly deficient in comparison with central nervous tissues. It is above all in the realm of their biochemistry and histochemistry that the sensory ganglia must be regarded as largely unexplored territory. Thus, for example, the peculiar vulnerability of the sensory ganglia to thiamine, pyridoxine and particularly to pantothenic acid deficiency will only be understood when appropriate biochemical and histochemical investigations have been conducted in both the normal and vitamin deficient animal and the results so obtained correlated with the histopathological appearances.

While the functions of pseudo-cholinesterase in nervous tissues remain ill-defined and as yet the subject of speculation, it may well be that this enzyme merits particular attention in the sensory ganglia in that these structures contain the enzyme in nerve cells rather than in white matter and also in cells that are devoid of synapses. In view of these facts, biochemical studies of the ganglia under influences such as peripheral nerve stimulation, nerve section or pseudocholinesterase inhibitors would be of particular interest and value.

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FROM THE PSYCHIATRIC CLINIC AT THE UNIVERSITY OF GOTHENBURG
(PROFESSOR BENGT J. LINDBERG, PSYCHIATRIST-IN-CHIEF)

IS HEREDITARY DIABETES INSIPIDUS OF NEPHROGENIC TYPE ASSOCIATED WITH MENTAL DEFICIENCY?

By

HANS FORSSMAN

Mental deficiency, as we all know, is a symptom of many different kinds of disorder. The same injurious agents that cause cerebral lesion and dementia in the adult cause mental deficiency or mild degrees of mental retardation in the child. This is especially true of infants who have not acquired many abilities. In one group the injurious agent is of environmental nature, or exogenic. In another it is of hereditary, or endogenic nature. It has been known for some time that there are a large number of different genes that can cause mental deficiency. Some of them have other effects in addition to defects in mental competency, and many of this category have been given thorough study, e.g., the one which also leads to the excretion of phenylpyruvic acid in the urine and the ones leading to the two forms of amaurotic idiocy. In other cases in which the hereditary disorder is not characterized by specific features of this type, many of the genetic conditions have not been satisfactorily worked out. There is reason to assume that mental deficiency, particularly of mild degree, is due to the operation of simple recessives and dominants, but we do not know how many there are of these genes and it is not possible to give an exact hereditary outlook for a separate case. Furthermore, in the separate case it is often difficult to distinguish between what is of environmental and what is of genetic origin.

Our present knowledge concerning the hereditary background of mental deficiency can be likened to the beginning of a game of spillikins or jackstraws. There are some straws at the edge of the heap which are easy of access, but nearer the center of the problem there is such a confusion that the utmost patience is required to be able to remove a single straw. The only way to get any further is to expose

straw after straw until the confused heap of genes causing mental backwardness is pulled apart. This is my reason for presenting a hypothesis to explain the mental deficiency in a few cases, namely the mental defect observed in connection with the so-called nephrogenic form of hereditary diabetes insipidus.

There are at least three different forms of hereditary diabetes insipidus, differing either in the way they are inherited or in their pathophysiologic characteristics. A simple dominant gene was described by Adolph Weil (1884), Lauritzen (1893), Alfred Weil (1908), Ellermann (1939) and several others. With this hereditary pattern the syndrome responds to pituitrin. A recessive, sex-linked gene, likewise responsive to pituitrin, was described by me in 1945.

This article is concerned with the third form of diabetes insipidus. This form is also characterized by a recessive, sex-linked pattern of inheritance, but differs in the important fact that the symptoms do not respond to the antidiuretic hormone, no matter how much is given. In 1942 I made a preliminary report of a family who had this form of the disorder. In 1945 Waring, Kajdi and Tappan described similar pituitrin-refractory diabetes insipidus in six children, all boys. Three of them were half-brothers but the authors did not study the hereditary background of the cases in any detail. The same year I made a fuller report of the 1942 family; at that time three male members with the disorder had proved to be unsusceptible to pituitrin. Williams and Henry (1947) published the same observation independently of me and suggested that the disorder be called "nephrogenic diabetes insipidus". This name was adopted by later authors on the subject. Two brothers showing the same disorder were described by Guard (1953) and sporadic cases of boys with the same clinical picture were reported by Macdonald (1953) and Yun-Chen Kao and Steiner (1953). Finally in 1954 I summed up what had hitherto been observed of the syndrome. However, then I did not discuss the intellectual retardation often associated with the disorder.

As regards the physiologic mechanism in this peculiar and rare form of diabetes insipidus, I shall only say this: one is forced to assume that in these cases the fault does not lie in the supra-optico-hypophyseal system as it does in the more common forms, but in the effector organs for the antidiuretic hormone—the kidneys. According to one hypothesis, in this form of diabetes insipidus there is a hereditary defect in the nephrons in the sections where water is re-absorbed, whence the adjective nephrogenic. As yet this hypothesis has not been confirmed by anatomic observations. The nephrogenic form of diabetes insipidus is characterized by unusually severe signs and symptoms,

and the patients have no power to concentrate their urine, not even to the slight extent seen in the other forms of the disorder. When they are deprived of water, therefore, their bodies dry up rapidly. This point is essential to my reasoning later on.

The association of diabetes insipidus with mental defects was noted in a few cases in the older literature[1]. Of these I shall mention the ones of McIlraith (1892) and Ehrmann (1911) because their pedigrees, though they do not permit definite genetic conclusions, nevertheless tally completely with a recessive, sex-linked pattern of inheritance. McIlraith spoke of "dulness of intellect, not amounting to idiocy" in three related boys suffering from diabetes insipidus. Ehrmann described three brothers with diabetes insipidus who made poor progress at school, the younger of whom he called imbecile. Two sisters of the brothers showed normal water metabolism and were well equipped intellectually. These two articles were published before it was possible to test with pituitrin, which was not discovered until 1913.

My own material is composed of one large and one small family tree and one sporadic case. It has not been possible to connect up the two trees nor either of them and the sporadic case. The conclusion that it is based on a recessive sex-linked gene is founded only on the larger of the trees and on support from the literature. Because of the clinical correspondence between all the cases treated in this article it is assumed that it is a question of the same mutation.

Figure 1 depicts the larger of my pedigrees where it is seen that affected subjects occur in four successive generations. All these subjects were men. In no case did the disorder pass from father to son; a woman always conducted the gene. The tree is typical of the recessive sexlinked pattern of inheritance. Four of the afflicted members were tested to see how they reacted to pituitrin and all of them proved to be totally unresponsive. This matter was discussed in my article of 1954. From now on I shall confine myself to the question of the mental level of the afflicted persons.

II: 2, 1854 -?. The presence of diabetes insipidus is confirmed by two hospital records for III: 5, one written in 1897, the other, which contained an independently recorded history, in 1905. Nothing is said about the intellectual level of this subject in the records. His home parish records state that in 1872 he ran

[1] I am not taking up in this connection the syndrome named after Lawrence, Moon, Bardet and Biedl, which is genotypic and which is sometimes but not always associated with diabetes insipidus and/or oligophrenia. However, it is also associated with a number of other disorders which do not occur in the cases I shall describe, e.g., adiposity, sexual retardation, syndactylism or polydactylism and atrophy of the optic nerve.

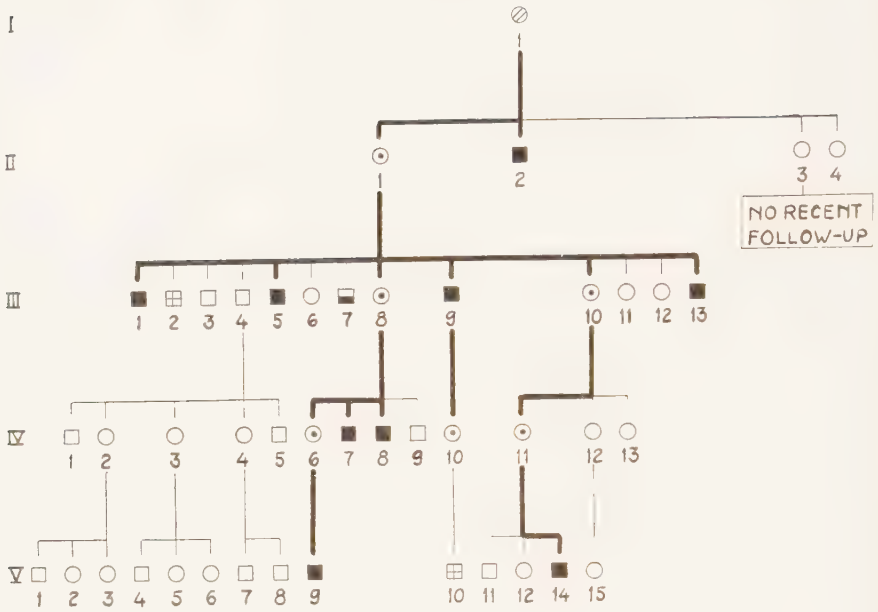


Fig. 1.
Explanation of symbols at the end of the article.

away from work to enlist as a soldier in Stockholm. The Stockholm parish catechization list states that he "knew the catechism passably and partook in Holy Communion". In 1879 he entered the police force. A year later he was given official warning for neglect of duty and a few months afterwards he was discharged from the force. He was finally transferred to the list of persons of unknown domicile and all track of him was lost. In my opinion, the information available does not indicate that he was mentally defective. The fact that he was employed as a policeman, even though he proved to be unsuitable, shows that he could hardly have had a severe mental defect.

III: 1, 1872–1936. This man suffered from clinically verified diabetes insipidus, not tested with pituitrin. He was noted to be imbecile in the Uppsala University Hospital where "mentally retarded since childhood" was recorded. The parish books record him as "idiotic". There the term is not used in the medical sense, more to denote severe mental deficiency in general.

III: 5, 1879–1905. This man had clinically verified diabetes insipidus, not tested with pituitrin. The record at the Uppsala University Hospital contains the remark "poor intellectual development". In the parish records he is described as "idiotic".

III: 9, 1888–1953. This man had clinically verified diabetes insipidus of nephrogenic type. I met him on several of his visits to the hospital, the first time when he was 53 years old. He was obviously feeble-minded, but he also had a prolonged schizophrenic psychosis with delusions and mild hallucinations. According to the records he suffered from primary mental deficiency and made poor progress at school. His intelligence age was 14 according to the Swedish point scale method (Wahlen) which corresponds to one of 13 according to the Yerkes, Bridges and Hardwick point scale method.

III: 13, 1896–1898. This boy died at the age of 2½ years. The diagnosis of diabetes insipidus is based on the convincing testimony of several siblings, but it was not clinically verified. However, his remarkable thirst is mentioned in the 1897 hospital record of III: 5. It is not possible now to get any data on his psychomotor development and his intellectual level cannot be estimated.

IV: 7, 1914–1915. This boy died at the age of 1½ years. The mother is living. The diagnosis of diabetes insipidus may be considered established. The mother consulted a physician, now dead, because the child drank so much. She had another son with the disorder and two healthy children and is quite certain that the two affected sons acted exactly the same way when they were small. Naturally, however, it is impossible to say anything about the intellectual level of such a small child after so much time has passed.

IV: 8, 1921– . The patient has clinically verified diabetes insipidus of nephrogenic type. When he was 9 years old he came to the Children's Department of the Uppsala University Hospital. His mother said that after a "severe intestinal disorder" at the age of 3 months, he was always delicate and fell behind in development. He did not learn to walk until he was more than 2 years old. I have met him several times and he has always given me the impression of being slightly feebleminded. After he had grown up I wrote "mental deficiency" in his hospital record. Unfortunately, however, he was not given any psychometric tests because at the times I saw him I had not yet become interested in the mental aspect of the disorder in question. However, I have just learned from his school in Uppsala that he made normal progress there. Accordingly, it is not certain that he is mentally deficient. In my opinion, however, he is at the most of low normal intelligence.

V:9, 1941– . The patient has clinically verified diabetes insipidus of nephrogenic type. He was admitted to an institution for feebleminded, where his I.Q. was calculated to be 69 according to Terman and Merrill.

V:14, 1944– . The patient has clinically verified diabetes insipidus of nephrogenic type. He had to start school a year late, and since then he has had to repeat a year. I met him when he was 9 years old and to me he seemed distinctly feebleminded. He was tested at a child guidance clinic in 1954 and his I.Q. was found to be 66 according to Terman and Merrill.

The family tree in which only two brothers are afflicted has not previously been published. It is seen in Figure 2. Assuming that nephrogenic diabetes insipidus is always inherited as a sex-linked recessive, I have only drawn the maternal lines of ascent. Naturally, however, nothing definite can be said about the manner of inheritance from this one pair of brothers. The father and his relatives are healthy. The many brothers and sisters of the mother are all healthy and have healthy children. This together with the fact that the disease is unknown in the foregoing generations indicate that the mother of the two afflicted brothers is the first mutant.

Number 1, born in 1943, has clinically verified diabetes insipidus of nephrogenic type. He gives the impression of being normally gifted; his teacher is of the same opinion and the Terman-Merrill test gives him an I.Q. of 99.

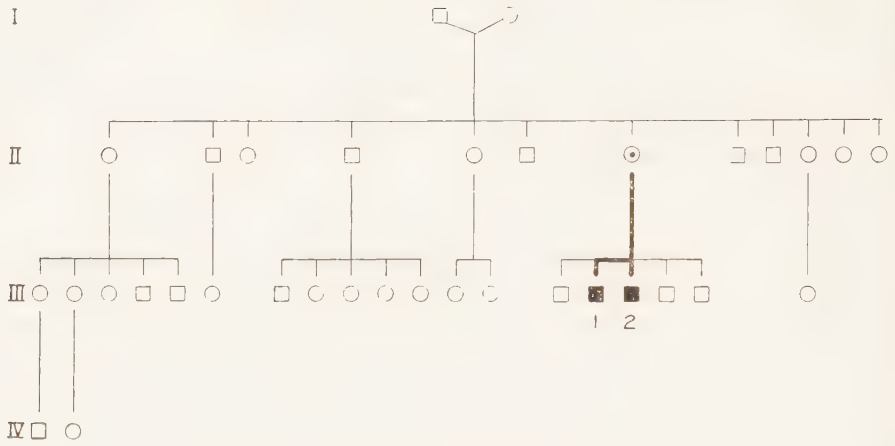


Fig. 2.
Explanation of symbols at the end of the article.

Number 2, born in 1944, has clinically verified diabetes insipidus of nephrogenic type. He gives the impression of being slightly feebleminded, and his mother says he is slow in understanding. His teacher says he should be put in a special class. According to the Terman-Merrill test, his I.Q. is 75.

Finally there is the sporadic case. His parents, whom I have met, are of normal intelligence. He has no brothers or sisters. No study has been made of the other members of his family.

He was born in 1948 and has clinically verified diabetes insipidus of nephrogenic type. At the age of 6, his Terman-Merrill I.Q. was 67, a figure which a child psychiatrist considered tallied well with the general impression he gave.

To summarize my material, it contains 12 males with diabetes insipidus of nephrogenic type. The resistance to pituitrin was tested in 7 of the cases. There is definite evidence of mental deficiency in 7 of the 12 cases. In 2 cases (III: 13 and IV: 7) nothing can be said about the intellectual capacity of the subjects because they died too young and too long ago. In another case (II: 2) conclusive evidence of a defect in intelligence was lacking. Two other patients had normal intellectual powers, but one of them (IV: 8) was previously diagnosed as mentally deficient and is probably of low normal intelligence.

Before interpreting these observations it must first be determined whether or not the combination was due to pure chance. In my publication of 1945 I noted that the 5 patients I was then able to examine in the family depicted in Figure 1 all showed some degree of mental deficiency. However, I had not systematically examined the mental capacity of the other members of the family and I was consequently in doubt as to whether it was a question of a causal connection or a

pure coincidence. Since then I have met four more persons with nephrogenic diabetes insipidus, three of whom were clearly feebleminded and this has led me to believe more in a causal connection. The mental ability of the healthy members of the family must naturally be considered when discussing the possibility of a genuine combination.

Here I am forced to rectify a statement in my monograph of 1945. There I said that mental deficiency was also common among the nonafflicted members of my families with diabetes insipidus. This is true only as regards one of the families, the one with an autosomally inherited, non-nephrogenic form of the disorder, which family is not treated in this article. Two of the sufferers from diabetes insipidus in this family were feebleminded, but so were a number of others who had no disorder in water metabolism. As regards the family depicted in figure 1 herein, the woman IV: 2 is reported to have had difficulty at school and a slight defect in intelligence. The sisters III: 6 born in 1880, III: 10 born in 1888 and III: 12 born in 1894 were all hospitalized for schizophrenia at some time during the years 1914 to 1929. They had all died before I came into contact with the family. I have read their hospital records and in each instance it is expressly stated that the subjects were of normal intelligence. All the records also state that they made normal progress at school and objective proof of this was included in each case. The record of one of the sisters relates that a maternal granduncle, i.e., a member of generation I in the figure, was feebleminded. It is not possible, however, to exclude the possibility that this man had diabetes insipidus; he is so situated in the tree that he might well have been afflicted. As for the other brothers and sisters, I have personally met III: 4 who is a surly eccentric person (note the many instances of schizophrenia in the family) but normally gifted. I met III: 8 several times during many years; she had a good mental capacity. Of generation IV I have met numbers 2 and 3. Number 2 is slightly feebleminded and had difficulty at school. Number 3 has a good mental capacity. Number 5 is getting along well at a technical university, according to two of his sisters. I know number 6 well; she is well developed mentally and does qualified office work. Number 9, whom I have also met, is an intelligent industrial worker. Finally, I have also met numbers 10, 11, 12 and 13 all of whom are of normal intelligence As for generation V, I know numbers 4, 11 and 12 all of whom are well equipped mentally. According to my contacts in generation IV, so far all the children in the fifth generation have made normal progress at school. I have not done any intelligence testing of the healthy members. Accordingly, among the nonafflicted of these five generations, there is one case of mild but unequivocal mental deficiency and another one three generations back, but the possibility of the latter having suffered from diabetes insipidus cannot be excluded.

Turning to the family in figure 2, I have met the three healthy brothers, the mother and maternal grandmother of the two afflicted brothers; they were all normally developed and gifted. As regards the other members of the family, I have only the testimony of the mother (who gave the impression of being reliable). She said that they were all normally gifted; none of them have had difficulty at school, and they are all normally developed.

The only other article on nephrogenic diabetes insipidus in which there is specific information on the mental capacity of the subjects is

that of Guard (1953), in which it is stated that one of the boys had an I.Q. of 73. But this result was obtained about a month after a severe cerebral injury with fracture of the skull. One of the afflicted members in Williams' and Henry's family was a physician, however, and so he must have been of normal intelligence.

The fact that so many of my patients with nephrogenic diabetes insipidus suffered from unequivocal mental deficiency while the rest of their families, with rare exceptions, were of normal intelligence has convinced me that a causal connection is present. As to the nature of the connection, it is only possible to conjecture.

One possibility is that it is a question of a pleiotropic gene which affects both the nephron and the brain. Human genetics contains several examples of pleiotropia of this nature, e.g., Marfand's syndrome. The hypothesis of pleiotropia is compatible with the fact that not all sufferers from nephrogenic diabetes insipidus are feebleminded.

However, there is another hypothesis which seems more plausible to me. According to this, the mental deficiency is secondary to the diabetes, being caused by the severe dehydration to which many of the subjects are exposed as infants. The disorder in water metabolism, which is unusually intense in the nephrogenic form, is present from birth. Infants are given a great deal of fluid, but when as in these cases there is an enormous need of fluid and when the child is so small that it cannot make itself understood, no steps are taken to give him an extra amount. In cases V: 9 and V: 14, which I have followed from early infancy, the child suffered during the first three years from severe dehydration and an intermittent high fever, the origin of which remained obscure for a long time. Both the children were hospitalized for long periods of time and the hospital records report severe nutritional disorder, dehydration and inexplicable fever. A few more cases will serve to illustrate this fact.

III: 2 died only a month old from an unknown disease, according to the parish records. III: 7 died at the age of 1 year and 6 months; according to the parish books, he had been delicate since birth. One of his sisters says that he had the "thirst disease" but I have not dared to mark him with more than a half-filled symbol, which means possibly afflicted. III: 13 died at the age of 2½ years from what was called meningitis; this diagnosis was not corroborated by autopsy. IV: 7 also died at home at the age of 1½ years of what was called a blood disease. V: 10 died at the age of four months in a pediatric ward from an obscure fever disease which autopsy could not fully explain.

All the last-mentioned were so situated in the family tree that they had a fifty per cent chance of getting the disease. Infants die from many causes, it is true, but there is not a single instance throughout

this family of a girl dying at such a tender age. Finally, we have the two severely dehydrated boys who survived and who now suffer from nephrogenic diabetes insipidus *and* mental deficiency. It seems to me to be a reasonable hypothesis that the dehydration in infancy causes a cerebral lesion which leads to mental deficiency. It can hardly be good for the brain to be dried out for a long time or to be exposed to the intoxication which results upon dehydration. But it must be emphasized once more that so far this is only a hypothesis.

I shall now turn to the two afflicted members who were normally gifted mentally. Case IV: 8 in the family depicted in Figure 1 was the second child in his family with diabetes insipidus. In the first case the parents had followed a physician's advice to keep to a strict diet and avoid giving the child extra fluid. This child having died, it was decided in the next case to do the opposite, and IV: 8 was given an extra amount of water from the start. Number 1 in the family of Figure 2 has been allowed to drink as much as he wanted from the beginning and his abnormal thirst was soon detected by his intelligent mother. It is conceivable that the generous supply of fluid in these two cases prevented dehydration and explains their good condition at present. However, the younger brother in the small family was also allowed to drink as much as he wanted and yet he is slightly feebleminded. If my hypothesis is correct and applicable to him as well, something else must have made his water metabolism worse.

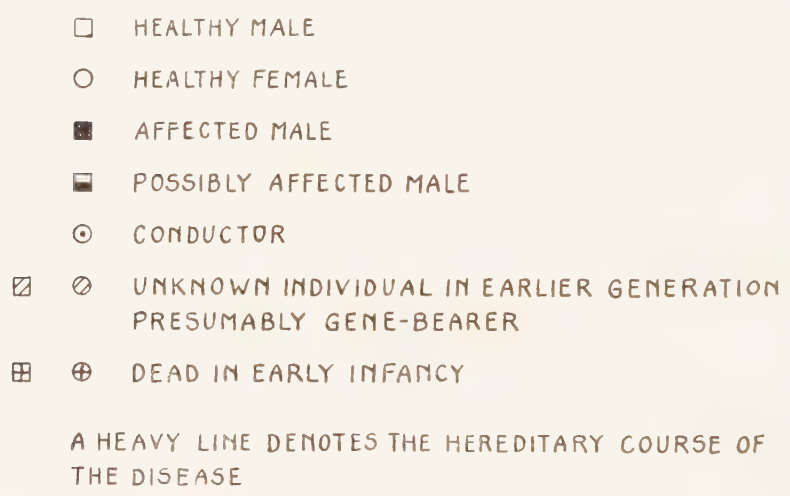
Hereditary diabetes insipidus is mostly a harmless anomaly which does not affect the general state of health or working capacity or give much trouble to the persons afflicted. On the other hand, the nephrogenic form, one aspect of which I have just described, is a severe disease. The risk of inheritance is large and easy to express in exact figures; 50 per cent of the boys of a conducting mother will be afflicted and 50 per cent of the daughters become conductors in turn. Considering the unhappy results of the disorder in the larger of my families, the heterozygotes and likewise the afflicted men should naturally be given permission for sterilization if they so want.

SUMMARY

An analysis as regards mental capacity is made of 12 males with hereditary diabetes insipidus of nephrogenic form, i.e., the type which does not respond to the antidiuretic hormone. The material is comprised of 9 afflicted members in four generations of one family, two brothers in another family and a sporadic case in a third. Seven of the 12 men suffered from mental deficiency and 2 were of normal

intelligence; it is not possible to say anything about the intelligence of the remaining 3. The families of the afflicted men showed no general tendency to mental deficiency.

The author is inclined to believe that there is a causal connection between the nephrogenic form of diabetes insipidus and the mental deficiency with which it is so frequently associated. He discusses two hypotheses to explain this connection. The first one is that it is a question of a pleiotropic gene. The second is that the mental deficiency is secondary to the dehydration occurring in infancy. The author favors the latter hypothesis and describes a few cases which bear it out.



Symbols.

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REFLEX-CHANGES AND OTHER NEUROLOGICAL SYMPTOMS IN FOCAL CORTICAL EPILEPSY

By

ANDERS CHR. GOGSTAD

INTRODUCTION

The present study was prompted by findings in a number of patients suffering from focal cortical epilepsy, asymmetries of tendon and cutaneous reflexes as the only neurological signs in the interictal periods. Among these patients a relatively large number presented no clinical evidence and no electroencephalographic signs of involvement of the motor cortex or pyramidal tract. In the light of data brought forward by recent anatomical and physiological research it was deemed worth while to subject this material to a closer analysis with the aim of determining the frequency of reflex asymmetries, i.e. unilateral "pyramidal" reflex symptoms, in cases of focal cortical epilepsy. In addition it was hoped that an analysis of this clinical material might yield some information of the central course of the reflex arcs.

As far as can be judged from available literature, little interest appears to have been devoted to the occurrence of constant unilateral "pyramidal" reflex changes, correlated to the electroencephalographic and other clinical findings in patients suffering from focal cortical epilepsy. *Gibbs & Gibbs* (1952), however, report hyper- and hyporeflexia among other neurological symptoms in their material of patients with focal cortical EEG signs, but no mention is made of asymmetries, nor do the authors distinguish between myotatic or cutaneous reflexia. Detailed investigations on this subject have not been published, as far as is known.

It is well-known to neurologists that disturbances of motor functions such as reflex changes, retardation of movement and changes in muscle tone may be seen not only in lesions of the "motor" regions or the pyramidal tract in the classical sense. Symptoms of this kind have

thus been described in lesions of the parietal lobe in experimental investigations of monkeys by *Kennard & Kessler* (1940), (see also *Peele* 1944 and *Tower 1949)*. On the basis of clinical observations *Monrad-Krohn*, as early as 1918, put forward the assumption that the arc of the abdominal reflex might involve the parietotemporal region. Lassek (1944, 1950) has presented further evidence on the discordance between "pyramidal" signs and pathological signs of affection of the pyramidal tract and motor cortex. *Monrad-Krohn* (1948, 1952) also points to the not infrequent observation of discrepancy between good motor functions and marked "pyramidal" reflex changes in cases of "pyramidal" lesions. "Pyramidal" symptoms without known affection of the structures mentioned have most frequently been reported in cases of tumours, also of the temporal lobes (for references see *Bailey* 1933, *Paillas & Tamalet* 1950, *Freeman, Manosous & Henderson* 1953, and *Strobos* 1953).

Experimental research has brought forward new facts which make necessary a thorough revision of the conventional concepts of the pyramidal tract, of its anatomical organization as well as of its functional aspects (for references see *Tower* 1949, *Brodal* 1953). Of relevance for the problem concerning us here is particularly the demonstration by *Levin & Bradford* (1938) that some 20 % of the fibres in the pyramidal tract in the monkey originate from the parietal postcentral regions (see also *Peele* 1942), and the recent demonstration of pyramidal tract fibres from the cortex of the temporal and occipital lobes, passing even to the lumbar segments of the spinal cord *(Walberg & Brodal* 1953). The latter authors suggest that damage to these fibres and to the ascending pyramidal tract fibres demonstrated by them (*Brodal & Walberg* 1953) and by *Brodal & Kaada* (1954) may contribute to explain the occurrence of a positive Babinski sign in "non-pyramidal" lesions.

MATERIAL AND METHODS

Nearly all patients treated in the Neurological University Clinic's Subdepartment for Epilepsy are non-institutional cases, who stay in the department for some days or weeks for the purpose of diagnostic classification. Of a total number of 427 patients registered in the department during the period from Jan. 1st, 1952, to June 15th, 1953, 201 (117 men and 84 women) showed clinical and EEG symptoms of focal cortical epilepsy. This number does not include cases showing evidence of foci in deep medial structures, cases of so-called kryptogenetic epilepsy, cases with diffuse cerebral disease and cases in which the

diagnosis has been uncertain. The duration of disease in all patients investigated is seen from Table 1, where the patients are grouped according to age. No patient is less than 8 or more than 65 years old. Only 27, or 13.4 % are more than 50 years of age.

TABLE 1

The material of the present investigation grouped according to age of the patients and duration of disease.

Duration of disease	Age groups			Total no. of cases
	8-14 years	15-49 years	50-65 years	
Less than 2 years	10	31	4	45
11–19 „	1	35	1	37
3–10 „	14	57	10	81
More than 20 „	0	26	12	38
Total	25	149	27	201

The clinical examinations have been performed in interictal periods, and repeated control examinations have been carried out with days' intervals by different members of the trained clinical staff of the department. The neurological examinations, including the reflex controls have been performed according to the technique described by *Monrad-Krohn* (1948). Uncertain and discordant observations have been counted as negative.

The EEG registrations have been performed in the EEG laboratories of the Neurological University Clinic of Oslo, by means of two 8 channel Kaiser apparatuses. The technique employed has been the conventional one with 16–22 electrodes in monopolar "average", as well as bipolar recordings. In all registrations flicker stimulation and five minutes' hyperventilation have been performed routinely. In doubtful cases repeated registrations have been made, either during seconal-induced sleep, or during activation by means of Pentazol.

The same technical personnel has been employed for all registrations. The electroencephalograms have been interpreted by Dr. G. F. Henriksen and Dr. A. Lundervold.

Supplementary investigations. X-rays of skull and spine, blood-, urine-, and cerebrospinal fluid-analysis have been carried out in all cases. Pneumo-encephalography according to the technique of *Robertson* (1940, 1946) has been carried out in 130 cases with interpretable findings. The encephalograms have been interpreted by the neuroradiologist Dr. A. Engeseth.

Classification according to cerebral localization. The cases have

been subdivided into 4 groups according to cerebral localization for the purpose of separating cases with foci in cortical regions generally presumed *not* to subserve motor functions (e.g. the temporal and occipital lobes) from those having foci in regions known to have such functions (e.g. the central and parietal regions). This classification according to localization differs from that generally used in EEG works and reviews.

Under the heading "frontal" are registered all cases with foci in the frontal lobe, the pre-central motor regions excepted. The "motor-parietal" group includes cases having foci in the pre-central motor region, the post-central and true parietal areas, together with all cases with foci on the border of the frontal, temporal and occipital regions difficult to localize more precisely to one or the other region. The "temporal" group includes foci in the true anterior, central and posterior temporal regions. The occipital group includes cases with foci in the occipital lobes.

With regard to the clinical classification of the cases the aura and initial symptoms have been particularly stressed, classification being made according to *Penfield & Kristiansen* (1951)[1], but also other clinical manifestations pointing to involvement of certain cerebral regions have been taken into account (for particulars see *Penfield & Erickson* 1941).

In each case the different components of the subjective and objective manifestations of the seizure have been carefully analysed and taken into consideration as possible indicators of the localization of the focus.

RESULTS

The EEG findings will be reported first and will serve as a basis of the further considerations concerning localization and symptoms. A survey of the EEG findings in all 201 cases of focal cortical epilepsy reveals that signs of one solitary focus were found in 167 patients. Of the remaining 34 cases the EEG was normal in 5 cases, general pathological activity without focal signs occurred in 7 cases, while EEG signs and clinical symptoms indicating more than one focus occurred

[1] For instance seizures with initial unconsciousness and simple adversive seizures have been considered as originating primarily in the frontal region, Jacksonian motor seizures and sensory somatic initial phenomena have been regarded as pointing to the Rolandic area and parietal lobe—autonomic motor and sensory phenomena to the Sylvian region or intermediate frontal region, psychomotor and various psychosensory phenomena as pointing to the temporal lobes, sensory visual phenomena as initial symptoms pointing to the occipital region.

in 22 cases, i.e. in 11 % of the total 201 cases. These 34 cases are not dealt with in what follows. In Table 2 are presented the EEG symptoms in the cases showing one solitary focus, i.e. the cases on which the present study is based.

TABLE 2

EEG findings in 167 cases with signs on one solitary focus.

	Focal epileptogenic activity	No focal epileptogenic activity	Total
Distinct focal pathological activity	94	31	125
General dysrhythmia with distinct focal signs	25	5	30
Bilateral synchron. activity with distinct focal signs	9	3	12
Total	128	39	167

125 cases, almost 75 %, show distinct focal activity only, with focal epileptiform activity in three fourths (94 cases). Focal epileptiform activity such a spikes, sharp-waves and paroxysmal bursts were registered in more than 75 % (128 cases).

To secure a correct localization of the epileptogenic foci, a correlation of EEG and clinical symptoms of localizing value is of the greatest importance. In Table 3 the cases with one solitary focus are listed according to cerebral localization based on the EEG records, to show the degree of accordance between EEG and clinical symptoms.

TABLE 3

Correlation between clinical symptoms and electroencephalographic signs, grouped according to cerebral localization of the 167 cases with a solitary focus.

	Focal clinical symptoms in accord. with EEG	No characteristic clin. sympt.	Total	Total %
Frontal	25	8	33	19.8
Temporal	67	18	85	50.9
Motor-parietal	38	4	42	25.1
Occipital	6	1	7	4.2
	136	31	167	100

A comparison of the clinical symptoms, initial and those occurring during the seizures, and the EEG symptoms, reveals that there is full accordance as regards localization in 136 out of the 167 cases, i.e. in

TABLE 4

Possible etiological factors grouped according to the results of the neurological examinations and to cerebral localization.

Etiology	No neurological signs				Reflex asymmetries only				Reflex asymm. + other neurological signs				Other neurol. signs without reflex asymm.				Total
	F	T	MP	O	F	T	MP	O	F	T	MP	O	F	T	MP	O	
Unknown or uncertain	4	28	8	1	2	12	3	2	2	3	3	–	–	–	–	–	68
Possible birth trauma	–	2	1	2	1	3	4	–	–	–	1	1	–	–	1	–	15
Tumour (non operat.)	–	–	2	–	2	1	–	–	1	–	3	–	–	–	1	–	10
Tumour (operat.)	1	1	–	–	1	1	–	–	–	–	4	–	–	–	–	–	8
Possible head trauma	12	11	3	–	4	17	2	2	1	1	1	–	–	–	1	–	55
History of encephalit.	–	3	1	–	–	–	1	–	–	–	–	–	–	–	–	–	5
Intracerebr. aneurysm	–	1	1	–	–	–	–	–	–	–	–	–	–	–	1	–	3
Thrombosis cerebri	1	1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	2
Abscessus cerebri (seq.)	1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1
Total	19	47	16	3	10	34	10	4	4	4	12	0	0	0	4	0	167

Abbreviations: F: "frontal" group
T: "temporal" group
MP: "motor-parietal" group
O: "occipital" group

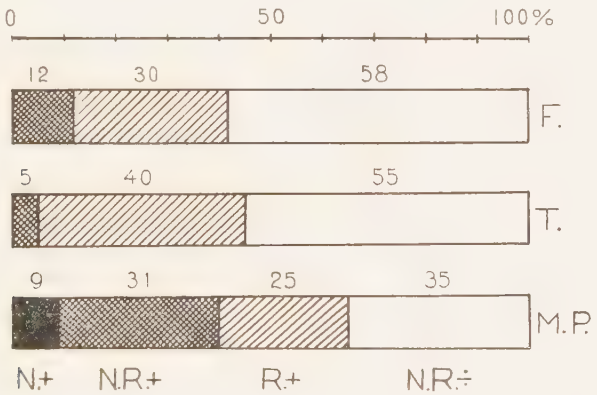
81.4 % of the total number of cases, while no characteristic clinical symptoms pointing to a certain cerebral region are found in 31 cases, i.e. in 18.6 %.

Temporal localization is found in 50.9 % of all cases while only 4.2 % show occipital localization.

In Table 4 the cases are arranged according to etiology. The cases are subdivided according to localization, as mentioned above. The table also gives the results of the neurological examination for the cases of each group.

As will be seen, in 68 cases, i.e. 40.7 % of the total, there was no evidence of known etiological factors in the case histories. There is a history of injury at birth or marked head trauma in 70, or 42 %, of cerebral tumour in 18, although only 5 in the frontal and 3 in the temporal regions, and of encephalitis in 5 patients only.

The percentage of cases presenting respectively (1) no neurological signs, (2) reflex-asymmetries only (i.e. unilateral "pyramidal" reflex signs), (3) reflex asymmetries combined with other neurological signs, or (4) such signs exclusively, is shown in Diagram 4 b.



It will be seen that no neurological symptoms were found in 58 % of the "frontal" cases (19 cases), 55 % of the "temporal" (47 cases), and in 35 % of the "motor-parietal" cases (16 cases). Reflex-asymmetries alone or combined with other signs were found in 42 % of the "frontal" cases (14 cases), 45 % of the "temporal" cases (38 cases), and 56 % of the "motor-parietal" cases (23 cases). Neurological signs apart from reflex-asymmetries were found in 12 % of the "frontal" (4 cases), 5 % of the "temporal" (4 cases) and in as much as 40 % of the "motor-parietal" cases (16 cases). Neurological symptoms with-

out reflex asymmetries present were not found in the "frontal" and "temporal" cases, but in 9 % of the "motor-parietal" cases.

The question to what extent cerebral atrophy occurs in a material of the present type is of some interest for the evaluation of the findings. Table 5 gives the result of pneumoencephalography in the cases of the four groups distinguished. The cases presenting reflex-asymmetries are listed separately from those presenting no asymmetries. Below in the table is listed the occurrence of general convulsions among the patients in the different groups. This is a feature of importance for the question whether possible secondary convulsory lesions may be responsible for the symptoms registered.

TABLE 5

Number of cases showing reflex-asymmetries as correlated with pneumoencephalographic findings and types of seizures for different localizations.

Ventricular system	Frontal		Temporal		Motor parietal		Occipital		Total
	R+	R−	R+	R	R−	R−	R+	R−	
Normal	4	7	18	18	5	6	3	1	62
Diffuse unilateral dilatation	0	2	1	4	2	0	0	0	9
Diffuse bilateral dilatation	0	2	1	8	1	4	0	0	16
Local, limited dilatation	3	3	13	9	8	5	0	2	43
Not examined, or inconclusive findings	7	5	5	8	7	4	0	1	37
									167
Type of seizure									
Grand-mal	9	13	26	35	14	10	3	3	113
Focal seizures and absences without history of grand-mal	5	6	12	12	9	9	1	0	54
									167

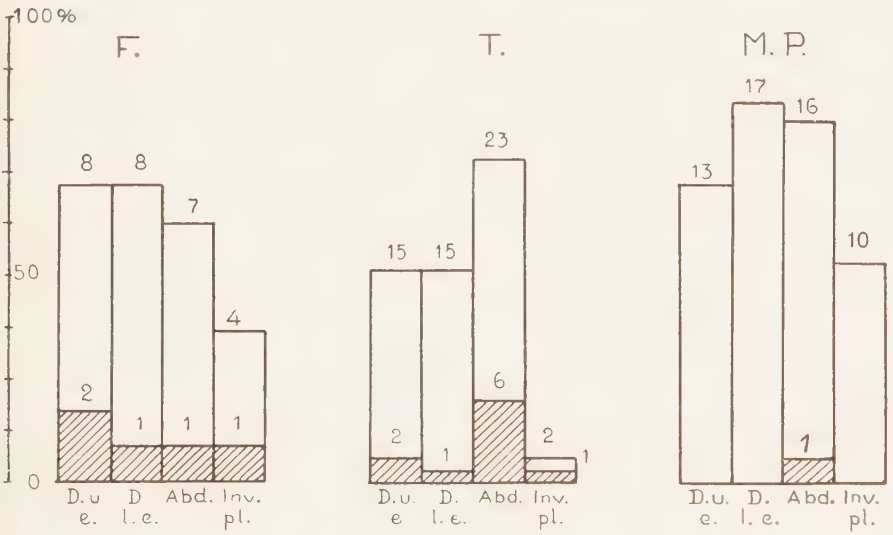
R+ Reflex-asymmetries present.
R— No reflex-asymmetries present.

Signs of generalized, bilateral or unilateral brain atrophy are found in only 25 of a total of 130 patients with interpretable encephalograms. Local limited expansions or asymmetries of the ventricular system, i.e. signs of a local atrophic processes, are found in 43 patients, or 32 %. A normal ventricular system is found in 48 %.

The number of patients who had never presented grand-mal seizures was relatively small,—accounting for only one third of the total. The

relative distribution of cases showing reflex asymmetries and the occurrence of negative status is, however, nearly equal in the group of patients without grand-mal and in the group of patients with grand-mal, i.e. neurological signs do not seem to be more frequent in the latter group.

The relative frequency of asymmetries of the different reflexes among the total number of patients presenting reflex changes is seen from Diagram 2. (Hatched fields indicate homolateral signs).



It will be noticed that simultaneous affection of several reflex qualities is present in a larger number of "motor-parietal" cases than of cases with other localizations. In the temporal group there are relatively fewer cases with affections of the tendon reflexes than in the other groups, and the plantar reflex is very seldom affected—only in 5 % (2 patients of 38). The abdominal reflex is almost equally affected in all groups. Particularly striking is the great difference between the number of cases with inverted plantar reflexes and weakened abdominal reflexes in the temporal group (5 % and 62 %) and the "motor-parietal" group (44 % and 70 %). It should also be noted that homolateral exaggeration of the tendon reflexes and weakened abdominal reflexes very seldom appear in the "motor-parietal" group, whereas varying from 5 to 16 % in the other groups.

Neurological signs other than reflex asymmetries were present only in altogether 25 cases—4 frontal, 4 temporal and 17 "motor-parietal" cases. Among the last mentioned cases were found 9 with

paresis of the 7th nerve, 1 with paresis of the 9th and 10th nerve, 1 with paresis of the 12th nerve, 6 with spastic hemiparesis, 5 with hemihypaesthesia, 1 with hemi-dyssterognosia, and 2 with dysphasia. Among the "frontal", paresis of the 5th nerve occurred once, paresis of the 7th nerve twice, paresis of the 9th and 10th also twice, and paresis of the 12th nerve four times, spastic hemiparesis and dysphasia occurred once. Among the four temporal cases 2 had paresis of the 7th nerve and 3 of the 12th nerve. No other motor or sensory symptoms were recorded.

DISCUSSION

The present investigations show that reflex asymmetries occur as the only objective sign in the neurological examination in a considerable number of patients suffering from cortical focal epilepsy and having a solitary cortical focus, either in the frontal, temporal or "motor-parietal" regions, without evidence of the presence of other cerebral changes.

Before entering on a discussion of the findings made and their possible significance, it is appropriate to consider to what extent it is permissible to draw conclusions on the basis of such a material as the present one. Obviously several objections may be raised.

The first question to be considered is whether it is permissible to regard the clinical and EEG symptoms usually called "focal" as originating from a focal anatomically localized lesion. It is generally accepted that focal cortical epilepsies are very often due to small cortical lesions (*Penfield & Humphreys* 1940, *Penfield & Steelman* 1947, to mention two papers dealing with cases verified at operation). However, in cases of focal cortical epilepsy due to birth injury more extended areas may be involved, as seen e.g. in the so-called "incisural syndrome" of the temporal lobe (*Earle, Baldwin & Penfield* 1953). In cases of neoplastic or vascular lesions, however, secondary pathological changes may often be responsible for the symptoms.

In cases of true focal cortical epilepsy, on the other hand, *i.e.* where there are neither clinical, nor pneumo-encephalographic signs of other cerebral lesions, but EEG findings pointing to a solitary focus, it must be justifiable to consider the epileptogenic focus as representing a comparatively limited cerebral lesion without considerable secondary pathological changes. In these cases, however, the possibility of secondary convulsory lesions must be taken into consideration. Thus *Scholz* (1951) describes cell-destructions in the cerebral and cerebellar cortices, thalamus, hippocampus, corpus striatum, the dentate and inferior olivary nucleus in patients having suffered

from general convulsive seizures. Widespread damage of this kind may also be thought to cause motor phenomena like reflex-changes. However, symptoms from other structures affected would be expected, such as from the basal ganglia, cerebellum and other cortical regions. Such symptoms were not observed among the patients presented in these series. Furthermore the reflex changes demonstrated occurred just as frequently in patients who had never had a single grand-mal attack. It seems likely, therefore, that secondary changes due to convulsions, are not responsible for the symptoms exhibited by the patients studied.

Furthermore, arteriosclerotic changes and other undiagnosed scattered lesions of traumatic, infectious, or vascular origin should be particularly taken into account when considering whether other cerebral lesions than the epileptogenic foci demonstrated, may be responsible for the reflex asymmetries in some of the cases.

The possibility of arteriosclerotic changes as being responsible may be almost excluded, since 86 % of the patients were between 8 and 49 years of age—*i.e.* in age groups in which marked arteriosclerosis is rare. While the occurrence of scattered lesions due to other disease processes cannot be frankly excluded in some cases, since there have been no postmortems, it can at least be stated that careful investigations did not produce anamnestic or clinical evidence in favour of this. On the whole, therefore, it appears justifiable to assume that at least in the great majority of cases used in the present study, the reflex asymmetries and other clinical findings have been due to focal cortical lesions.

A few more points deserve attention, for example the question to what degree the epileptogenic lesions are really anatomically circumscribed. The pneumo-encephalographic findings show that a normal ventricular system occurred in almost half of the patients. However, reflex changes were just as frequent in these cases as in those having diffuse or local dilatation of the lateral ventricles. This lends some support to the assumption that remote effects caused by diffuse atrophy and retraction were not to a greater extent responsible for the symptoms. The electroencephalographic findings also lend support to the assumption that the demonstrated foci were limited, because distinct focal cortical activity was shown in nearly three fourth of the cases.

Finally the possible sources of error and limitations in regarding the EEG findings as pointers to a distinct cerebral localization should be considered. There is conformity between the clinical and EEG findings as regards cerebral regional localization in four fifths of the cases, while in the remaining one fifth the clinical symptoms did not

point to any specific region. Cases with discordant clinical and EEG symptoms have been omitted. Again, this considerable conformity indicates that the EEG symptoms really did originate in the cerebral region from which they were registered.

Turning now to a discussion of the findings, attention will first be drawn to the more massive and evenly distributed reflex changes in the "motor-parietal" group, which accounted for about one fourth of the total. The Babinski sign also occurred more frequently in this group than in the others as did other neurological symptoms, while they were particularly rare in the temporal group. It must be noted, however, that the relatively large proportion of tumour cases in the group may to some extent be responsible for the frequent occurrence of neurological symptoms. However, after elimination of these cases, the same tendency is still obvious. The demonstration of the greater frequency of neurological symptoms especially of the motor type in patients of the "motor-parietal" group, is in conformity with our present knowledge of these regions as being chiefly engaged in motor functions. The group includes cases with lesions both in the pre-central motor region and in the parietal lobe, which is also known to be related to motor functions (e.g. *Tower* 1949).

Considering the "frontal" group of cases, it should be recalled that numerous investigations of the consequences of pre-frontal leucotomy and lobotomy do not reveal any lasting reflex-changes (see e.g. *Pool & al.* 1949, *Rose* 1950); neither do other traumatic lesions in the pre-frontal region result in constant reflex changes (*Rouquier* 1948). The reflex changes registered in this material in cases of the "frontal" group must therefore be presumed to have been due to lesions in the pre-motor area. This is in conformity with the finding that other neurological symptoms are slightly more frequent in this group than in the temporal group.

As far as the "occipital" cases are concerned, it is remarkable that very few patients had foci with this localization—only about 4 % of the total. The true occipital areas, however, are of rather moderate size when compared to the other areas of division used in this work. Larger materials, such as that of *Gibbs & Gibbs* (1952), make it clear that occipital foci are found most frequently in the age groups 0–5 and 5–10 years. In the present relatively small material no patient was less than 8 years of age, and the age group 8–14 accounted for about 12 % of the total, only. It is therefore impossible to draw any numerical conclusions from the cases in this group. In four of the seven "occipital" cases of traumatic or unknown etiology, however, constant asymmetries of the abdominal and tendon reflexes, were

found without other symptoms present—two of these having a completely normal ventricular system.

Particularly striking, however, are the results of the study of the temporal lobe cases, accounting for more than 50 % of the total. The high percentage of temporal localization in a material of focal cortical epilepsies is well-known from other and greater statistics. (*Jasper, Pertuiset & Flanigin* 1951, *Gibbs & Gibbs* 1952). In 45 % of the temporal" cases (37 patients of 85) reflex asymmetries were demonstrated —of the abdominal reflex in almost two thirds of these patients. In the light of the conventional concepts of the functions of the temporal lobe these observations are of considerable interest. Until recently it has been common teaching in clinical neurology that the temporal lobe does not subserve motor functions.

However, electrical stimulation of the subcortical temporal structures, nucleus amygdala, hippocampus and gyrus hippocampi, has been shown to elicit somato-motor reactions: conversive movements, general rigidity, contralateral increase of muscle tone (for particulars see e.g. *Kaada* 1951, *Penfield, Jasper & Feindel* 1952, *Kaada, Andersen & Jansen* 1953, and *Kaada, Jansen & Andersen* 1953). The literature on experimental, operative, or pathological lesions of the temporal lobe on the other hand, contains few data on reflex changes. Thus reflex changes are neither mentioned in the experimental works of *Klüver & Bucy* (1939) nor in the reports on operated cases of *Penfield & Flanigin* (1950), *Bailey & Gibbs* (1951) of *Green, Duisberg & Mac Grath* (1951), to mention a few. In cases of tumours of the temporal lobe, however, reflex changes have been observed in a number of cases, e.g. in the series of *Freeman, Manosous & Henderson* (1953), *Paillas & Tamalet* (1950), and *Strobos* (1953). *Rey, Pond & Evans* (1949) in a paper on temporal lobe function, report the findings in 26 patients suffering from temporal lobe epilepsy. Reflex asymmetries were present in the majority of cases, six of them showed a positive Babinski sign. In this connection it is appropriate to recall the theory that clinical and electroencephalographic symptoms registered as due to temporal lobe affections are partly derived from other structures than the cortex (a.o. *Penfield, Jasper & Feindel* 1952), such as the above-mentioned subcortical nuclei, from deeper medial structures or even from the contralateral temporal pole. The abundant inter-temporal and subcortico-temporal connections make a mechanism of this kind possible, as advocated by *Stoll, Marsan & Jasper* (1951) and *Marsan & Stoll* (1951). In the present material the conformity between clinical and electroencephalographic symptoms (67 out of 85 cases) and the lack of other neurological objective signs makes it unlikely that the

lesions have extended deeply enough to affect the pyramidal tract fibres proper. However, the deeper structures within the temporal lobe, especially certain sections of the amygdala and hippocampus, cannot be excluded as being co-responsible for the symptoms in a certain number of the cases. On the other hand, the function of the cortical-spinal fibres from the temporal lobe, demonstrated by *Walberg & Brodal* (1953), is unknown, and destruction of these cortical cells or interruption of their fibres may be considered as being of importance for the occurrence of the reflex symptoms demonstrated. Finally the possibility that a limited number of the lesions might involve the secondary motor area in the insular region or the Fissura Sylvii should not be overlocked, even if no evidence is available as yet showing that lesions in these regions cause motor release phenomena (see e.g. *Fulton* (1949) and *Penfield & Rasmussen* (1950).

In the temporal lobe cases it was a striking feature that abdominal reflex asymmetry occurred much more frequently than an inverted plantar reflex. This seems to confirm that the cortical arc of the abdominal reflex is more widespread than that of the plantar reflex, as indicated by *Monrad-Krohn* (1918, 1950).

As mentioned in the description of the findings, "pyramidal" reflex changes were sometimes observed *homolaterally* to the supposed epileptogenic lesion. Homolateral "pyramidal" symptoms in cerebral lesions are not unknown and have been discussed for example by *Lassek* (1944, 1950). In the present material homolateral reflex changes were observed in a percentage varying from 2.5 % to 16 % of the cases presenting unilateral "pyramidal" reflex symptoms, mainly in frontal and temporal cases. The number of cases is too small to permit any conclusions, but the observations are of a certain theoretical interest. Nothing certain is known concerning the pathways of the homolateral motor impulses. *Walberg & Brodal* (1953), however, found that some of the cortico-spinal fibres from the temporal and occipital lobe like those from the "motor" regions reach the homolateral side of the cord. These cortico-spinal fibres probably permit bilateral control of subcortical structures.

The present clinical material is insufficient to warrant more than some general suggestions, but in spite of its shortcomings it may, it seems, be taken to support some of the recent experimental studies on motor functions of the cerebral cortex. It appears from the present study that signs of "pyramidal" reflex changes, until recently assumed to be chiefly signs of involvement of the motor cortex or the pyramidal tract proper, obviously are not very rare in lesions of other cortical regions either. The findings may support the conclusion arrived at by

Lassek (1950) that there is no clear correlation between damage to the pyramidal tract or the motor area and clinical signs assumed to betray involvement of the pyramidal tract fibres, and are in agreement with the view of the pyramidal tract recently discussed by *Brodal* (1953).

SUMMARY

A material of 167 selected non-institutional epileptics, presenting clinical and EEG evidence of a solitary cortical focus, were investigated with regard to the occurrence of neurological signs, especially unilateral "pyramidal" reflex alterations.

The majority of cases were of "traumatic", "possibly traumatic", or "unknown" etiology. In none of the cases there were signs of other cerebral lesions than the epileptogenic one. In more than 80 % of the cases, there was full conformity as regards localization between clinical symptoms, especially aura and initial symptoms, and EEG signs.

51 % of the cases had foci of temporal localization, 25 % of motor-parietal, 20 % of frontal, and 4 % of occipital localization.

Reflex asymmetries were found in almost half of the cases, varying from 42 % of the frontal, 45 % of the temporal, to 56 % of the motor-parietal cases.

Homolateral pyramidal reflex changes were found in some of these cases (2.5 %–16 %).

Among the temporal cases unilateral decreased abdominal reflexes, mostly on the opposite side, were found much more frequently than a positive Babinski sign (60 % and 5 %, respectively).

Neurological symptoms other than reflex changes were found only in 5 % of the temporal, 12 % of the frontal, and 40 % of the motor-parietal cases.

Local or diffuse dilatation of the ventricular system, as revealed by pneumoencephalograms, or the occurrence of general convulsive seizures did not appear to be more frequent among cases presenting neurological symptoms, than among those with a negative neurological status.

A brief discussion of the findings in relation to the present knowledge of the motor functions of the cerebral cortex is given.

The series is too small to warrant more than general suggestions, but the findings in these clinical series seems to confirm the results of some recent experimental neurophysiological and neuroanatomical investigations, and justify the conclusion that there seems to be no complete correlation between "pyramidal" symptoms and pathological involvement of the motor cortex or pyramidal tract.

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INVESTIGATIONS INTO AUTONOMIC RESPONSES DURING EMOTION

By

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During recent years the practical study of autonomic responses to emotion in human subjects has followed several lines. Many exact investigations have been made to study the influence of emotions on clinical tests used in the diagnosis of systemic diseases, e.g. electrocardiogram, respiration, cardiac output. The results so obtained have only a secondary interest for the psychologist and the psychiatrist, mainly because the methods of provoking emotions in such experiments have, with a few exceptions, been inexact; their main purpose has been to imitate the situation in which an anxious patient under examination for an organic disease is submitted to one of these exact clinical tests. However, the problem has also been attacked from a more psychological angle. Many attempts have been made to differentiate between the responses to various types of emotion e.g. fear, anger, sorrow, and some important results have been obtained in this field. Further, the differences in the reactions of normal persons and of patients with various mental diseases, for example psycho-neurotics and schizophrenics, have been examined, but so far without important results. A fourth line of investigation has been the use of autonomic reactions as indications that a person is undergoing emotion. In particular, in U.S.A. the polygraph has been used extensively in the detection of crime. No detailed references to these important experiments will be given. The well-known work of *Cannon* (1953) and the comprehensive review by *Altschule* (1953) should be referred to.

Surprisingly enough, few attempts have been made to follow the autonomic response to emotion during a mental illness and to eva-

luate the effect of therapy by the frequency and intensity of such responses. The most important work along those lines so far published has been in the monograph of *Greenblatt* and *Solomon* (1953) on the effect of lobotomy. Some effect, though not a very pronounced one, was found on emotional reaction.

There are several reasons for the scarceness of investigations into this particular subject. Firstly, the response differs considerably from individual to individual, and the intensity of the autonomic response does not reflect the intensity of the emotion to any great degree. Moreover, the methods are elaborate and very difficult to standardize, especially the methods of inducing emotion in the subjects. This report presents an attempt to assess objectively the effect of treatment with a drug on the patients' control of emotions. It gives a general description of the technique used and the responses seen in untreated subjects. The effects of the drug tested will be recorded in a subsequent paper.

TECHNIQUE

The subjects examined were 6 patients under group-treatment for psycho-neurosis. The patients were told that the experiments were made to investigate the underlying causes of their disease, and that by means of a "lie detector" we should try to ascertain the thoughts troubeling them most. A series of normal subjects were submitted to the same test as a means of investigating "spontaneous" reactions in this experimental situation.

Experimental conditions.

The experiments were made in a sound-proof room whose appearance was made as pleasant as possible, with a rug on the floor, framed pictures on the wall and flowerpots in the windows. Only a psychologist and the patient were present in this room. The patient lay on a couch in the middle of the room, and was connected with the recording devices which were all placed in an adjacent room. The psychologist was in touch with the control room by means of head phones. A one-way screen made it possible to observe the patient from the control room. The psychologist was one of the leaders of the group therapy. She was very familiar with the patients' personal problems, and the patients had deep confidence in her. Each experiment lasted about an hour, including some twenty minutes in which the patient was intended to accustom himself to the surroundings. During this period ordinary neutral conversation took place.

Provocation of emotions.

Several methods have been used in earlier investigations to provoke emotional reactions such as prolonged interviews touching emotionally loaded themes (*Schou*, 1937); suggestions ("Think of something unpleasant") (*Finesinger*, 1939); word associations (*Greenblatt* and *Solomon*, 1953); films etc. In the present experiments we wished to submit the experimental subjects to periods of emotion alternating with neutral periods. To this end we decided to combine the interview method with the presentation of stories. The interview has several advantages. It is possible for the trained psychologist to regulate the emotional pressure according to the responses of the patient. The patients can be led slowly to the danger points in the conversation; if they react too violently it is possible to soothe them, while still keeping to the same topic. Slow reactions from the autonomic system can thus be obtained when the same topic is discussed for 5 minutes or longer. Finally, the patients' verbal expressions give good indications of the intensity of emotion provoked.

The interviewing technique has the disadvantages that the psychologist may find it difficult to control the interview sufficiently to get an objective result. Moreover, the experimental subject's spontaneous respiration cannot be recorded when he is talking. The patients were therefore asked to listen to some stories which had previously been recorded and were transmitted on a loud-speaker to give uniform presentation. In the first experiments these stories were 5–10 minutes long. Only three stories weer read per session, and no interview followed. In later experiments the patients were submitted to both stories and interview. Six stories, each lasting 1½–3 minutes were used. Five of the stories were intended to be neutral to the patient and were either based on popular "psychological situations" in a weekly magazine or on other patients' case histories. A 6th story placed at random among the other five was based on one of the subject's own problems. An example of such a personal story will be given below. The stories were separated by pauses of 1 minute, during which the patient was requested to think the story over so that he could prepare himself for the coming interview. A new set of stories, including one of emotional content, was used in each experiment. The necessary three or four emotional stories were all written before the first experiment and used in random sequence. After the stories had been read, they were discussed one by one. In this way the patient's emotional reactions to the stories could be explored and the psychologist was able to vary the emotional pressure exerted on the patient.

The interview was recorded on wire or tape, and the records of

the interview and stories were typed after the experiment. By means of a stop-watch, every 10 or 15 seconds were marked on the typescript. The various recording devices used during the experiment were synchronised by a signal system. One signal was given each minute. It was thus possible after the experiment to assess the time relation between any place on the typescript and the record of any autonomic response with a precision of a few seconds.

A series of emotionally stable and apparently normal subjects were tested by exactly the same technique, in order to find out how normal persons reacted in similar situations. After the stories had been read and discussed, the subjects were asked if they would agree to receiving a mild electric shock. All did and sham-electrodes were fastened to the free left hand. The subjects then heard a loud discussion between the technicians and the leader of the experiment about the intensity of the current that could be used, and were warned that the shock would be felt after the count of three. No shock was given, and the patients were told that this procedure was to test their reactions towards an expeced unpleasant event.

The recording of the autonomic reactions[1].

During the experiment, the skin temperature, the skin resistance, the pulse rate and the respiration were recorded.

The skin temperature was measured in the zygomatic area by means of a thermocouple or a thermistor (Standard Telephones and Cables, Ltd.). The temperature was recorded continuously photographically by means of a mirror instrument. Even small changes in the skin temperature were recorded immediately.

The skin resistance was measured with one zinc electrode placed directly on the dry palm, and the other (indifferent) electrode on the ventral side of the forearm. In order to avoid polarization, alternating current was used. The skin electrodes were placed in series with a resistance about 100 times as high as the highest possible skin resistance and the main current (50 cycles per sec.) was passed. A valve-voltmeter was shunted across the skin electrodes. The potential thus measured gives an expression of the resistance between the skin electrodes. The deflections of the valve-voltmeter can be calibrated if the skin electrodes are replaced by a known resistance. The variations in the main current were considerable, and for this reason a transductor was used. The variations in the main current passing the transductor

[1] Mr. *Tvede Jacobsen*, technical engineer, has given invaluable help in the construction of the apparatuses.

were recorded continuously, together with the current through the skin electrodes.

The respiration was measured by means of a bag filled with air and placed on the lower part of the chest and a volume recorder writing on a kymograph.

The pulse rate was recorded in the earlier experiments by a cuff placed round the calf and in the later experiments by an electrocardiographic device, from which the disturbing frequencies from the resistance current were filtered off.

After the experiment the pulse frequencies were counted for periods of 10 seconds and recorded on smoked paper. On the tracings of the respiration the intervals between inspirations were measured, and these figures were transferred to another smoked paper in the same way as the measured pulse frequencies.

The types of the autonomic reactions.

Changes in the autonomic tonus are considered as emotional reactions when they occur simultaneously with, or immediately after, "emotional" topics—that is, when the subjects said that they were emotionally involved, or when their voices or attitudes clearly indicated emotional tension. All other changes are considered as "spontaneous". It may be that some of these "spontaneous" reactions have an emotional background. But rather than attempt some subtle explanation of every reaction observed, we have tried to keep the interpretation of the curves on the safe side by the distinction mentioned.

The reaction of the skin temperature.

Initial reactions: most of the subjects showed an even increase in skin temperature at the beginning of the experiments. Examples of this are seen in Figs. 1 and 2.

Even and prolonged increases other than the initial ones were not seen later in the experiments, unless emotionally loaded topics had been discussed. Two curves were characterized by a sharp and sudden increase during the initial "non-emotional" period (e.g. Fig. 5).

The fright reaction: When the subjects were asked to take an electric shock, 6 out of 7 responded with a drop in skin temperature. Sometimes the temperature increased again to its former level. The curve given in Fig. 1 shows this phenomenon.

Emotional reactions: The reactions to the transmission or discussion of emotionally loaded topics were generally characterized by rather steep increases, from 0.3° to more than 2° over ½–2 minutes

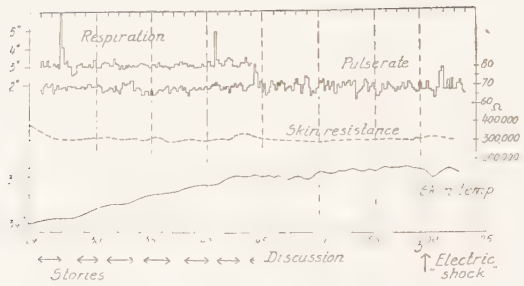

Fig. 1.

Experiment No. 139. Autonomic reactions of a normal female under experiment, aged 31 years.

Abscissa: Time in minutes.

Ordinate: As indicated.

The respiration curve shows the length of each respiration, but is modified so that only the average and the extremes are given. At the arrow the subject was warned that she would receive an electric shock.

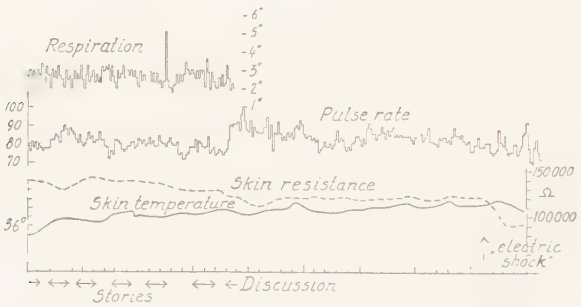

Fig. 2.

Experiment No. 135. Autonomic reactions of a normal male under experiment.

Abscissa: Time in minutes.

Ordinate: As indicated.

The respiration curve shows the length of each respiration, but is modified so that only the average and the extremes are given. At the arrow the subject was warned that he would receive an electric shock.

(Figs. 5 and 6). Sometimes, especially when emotionally loaded topics were discussed for a longer time, the increase was less steep, but prolonged for several minutes, until the discussion was changed to a more neutral topic. Curves of a similar type have been given by *Schou* (1937).

The pulse rate.

Effects of mental activity: Mental activity generally results in an increase in pulse rate; e.g. when subjects are asked to add numbers

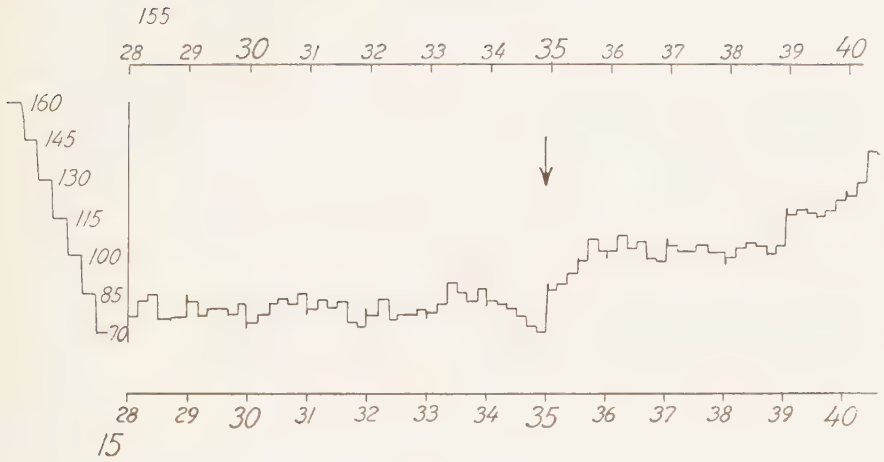

Fig. 3.
Increase in pulse rate during addition of numbers beginning at the arrow. The pulse rate is measured in 10 seconds periods, but calculated at the rate per minute (ordinate). Abscissa: time in minutes.

they respond with an increase of about 20 % (in our experiments ranging from 11 to 41 %). An example of such a response is given in Fig. 3. By repetition of the experiments at 1 to 2 day intervals, this reaction was diminished: in the third repetition the increase was found to be only 10 % (range 0 to 18 %).

Fright reaction: A sudden unexpected noise, for example, a pistol shot, was generally followed by 2 to 10 heart beats 10 to 15 % faster than the rate immediately before the noise; after this there followed a few somewhat slower beats before the former rate was restored. When the fright was of a longer duration, for example, in the experiments in which the subjects expected an electric shock, they responded during this period with a prolonged increase of about 10 % (range 2 to 19 %) in the average pulse rate over a minute. Examples of this reaction are found in Figs. 1 and 2.

Reactions on emotion: In general, periods in which topics with an emotional significance alternated with topics of a more neutral content were characterized by more frequent and more intense variations than those seen during the neutral periods (Table 1).

The increase due to an emotional reaction can be sudden, but more commonly there is an increase lasting 20 to 60 seconds. When the pulse was recorded by means of a cuff, very frequently the pulse became uncountable during periods of strong emotion. Probably this was due to muscular tension.

All the normal subjects and two of the psycho-neurotics reacted at

TABLE 1

Variations in pulse rates of normal subjects and psycho-neurotic patients found during neutral periods and during periods of submission to emotions.

		Normals	Psycho-neurotics	
		Neutral periods	Neutral periods	Emotional periods
Number of persons		14	5	4
Number of experiments		37	12	9
Total duration of periods, minutes		365	169	327
Number of 10″ periods exceeding the previous 2′ level by	5 %	49(8.1)	27(9.6)	95(17.2)
	10 %	18(3.0)	6(2.1)	50(9.2)
	15 %	4(0.7)	1(0.4)	28(5.1)
	20 %	1(0.2)		19(3.5)
	30 %			5(0.9)
Number of 1′ periods exceeding the previous 2′ level by	3 %	27(4.2)	13(4.6)	84(15.4)
	5 %	15(2.5)	9(3.2)	69(12.6)
	10 %	2(0.3)	1(0.4)	28(5.1)
	15 %		1(0.4)	6(1.1)
	20 %			3(0.6)

The figures in parentheses give the average number per hour.

the beginning of the discussion with an increase in pulse rate. It is arguable whether this reaction is emotional or merely a sign of mental effort similar to the reaction seen during the adding of numbers.

The respiration.

The recording technique only permits determination of the length of each respiration and the ratio inspiratory: expiratory phase and to a certain degree the depth of the respiration. The type of respiration, for example whether abdominal or costal, cannot be assessed.

When a subject a resting or listening to a neutral story the duration of his respirations varied little. With shorter or longer intervals (1–5 min) a brief pause of 6–10 seconds was seen in the respiratory rythm. The respiration of psycho-neurotic patients showed no fundamental difference from that of normal subjects.

When a story of *emotional content* was read loud, the respiration generally became irregular, frequently owing to pauses of varying length between two series of respiratory movements. Taken as a whole, the respiratory rate was a little slower during an emotional period, usually because of a prolongation of the expiratory phase and the expiratory pause. In this way the ratio inspiration:expiration can be somewhat lowered during an emotional period, but this was by no

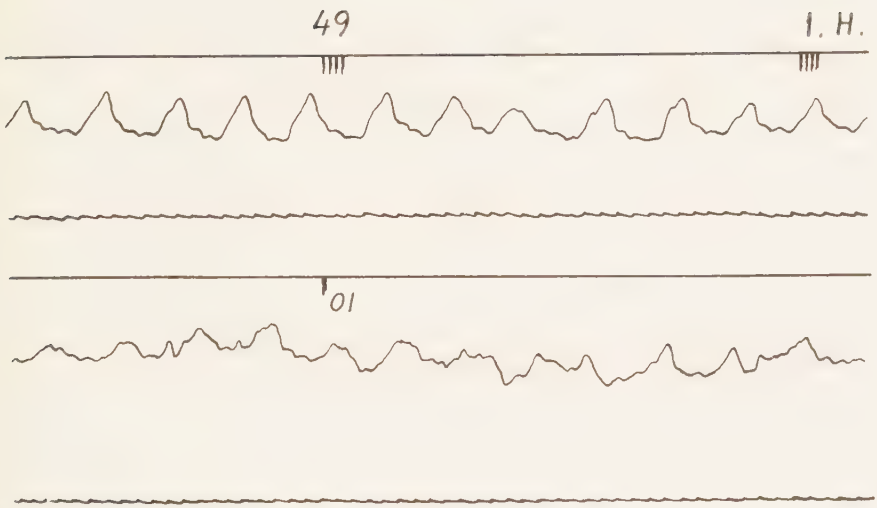

Fig. 4.

Part of the original tracings of respirations and pulse rate in experiment 122. The upper tracing is about 2.49 during an emotionally indifferent period, the lower tracings just after the patient has listened to a story with an emotional content (01 = 3.01 p.m.). The total experiment is given in fig. 5.

means a constant reaction. An example of the changes in the respiration during a story of emotional content is given in figure 4. However, the respiratory changes seen during these experiments generally were inconsistent.

Skin resistance.

The skin resistance in the palm varied considerably from person to person and from experiment to experiment in the same person. Most commonly the skin resistance was found to be 300,000 to 200,000 ohms, but the whole range was 1,000,000 to 100,000 ohms. During the emotionally neutral observation periods the resistance was generally found constant, but a slight and steady decrease or a increase followed by a decrease have been seen, the variation not exceeding 30 % of the initial value.

In 3 of the experiments, several small rapid falls of about 20 % were seen at intervals of about 3–5 minutes. There is no reason to believe that these changes had any connection with the subjects' emotions. No difference in the level or pattern of the skin resistance could be seen between the normals and the psycho-neurotic patients during the resting periods.

Fright reaction: The warning that the subjects were to receive an electric shock in most cases caused a sudden drop in the skin resistance (Fig. 2) and this sometimes gave place to a sharp increase when they realized that the "danger" was over. Two psycho-neurotic patients gave similar responses at the sight of the syringe when they were about to receive an injection. In both instances this reaction disappeared when the situation was repeated in the following experiment. In one experiment we succeeded in getting an idea of the intensity of the feelings underlying a pronounced psycho-galvanic response. During the measurement of skin resistance of one of the authors, the other investigators tipped a chair over in the control room and in their exchange of remarks hinted that one of the galvanometers had fallen down, but that nothing serious had happened. The experimental subject felt slight annoyance, but was by no means frightened. Nevertheless a pronounced psycho-galvanic reflex was recorded.

When the discussion of the stories began, two of the normal subjects responded with falls in the skin resistance (e.g. Fig. 2). This reaction was not seen among the psycho-neurotics.

Emotional reactions: The skin resistance was generally found constant; some patients showed a steady fall over the whole period when they were made to hear or discuss emotionally loaded subjects. One patient responded with a steep drop in the skin resistance from 225,000 to 150,000 ohms while listening to a story based on her own life (Fig. 6).

The experimental subjects and their reactions.

Apart from a few pilot experiments seven normal subjects and six psycho-neurotic patients have been examined.

Normal persons: The group of normals were four males and three females, all office workers, aged 28 to 43 years. A preliminary interview ensured that none of these subjects was or had been under treatment for "nerves" or psychosomatic diseases. Also those who stated that they had mental problems or worries or that members of their families were extremely nervous were discarded from the experiments. The normal subjects were only taken in experiments once. They were presented with six stories, all of which had proved to be emotionally loaded for patients. These stories were discussed afterwards. An abbreviated part of the discussion with a married woman of a story about a housewife who feels inadequate sounds as follows:

Psychologist: Do you remember the story about the family in the suburbs?

Experimental Subject: I think that her husband should have assisted her, when it was impossible for her to plan her work. How old were the children?

			During stories			Beginning of the discussion			During discussion			Frightening reaction			
Exp. no.	Sex	Age	Respiration	Pulse rate	Skin temperature	Skin resist.	Pulse rate	Skin temp.	Skin resist.	Pulse rate	Skin temp.	Skin resist.	Pulse rate	Skin temp.	Skin resist.	Remarks
135	m	30	regular	increase during first 5 min. later fairly constant	even increase during first 4 min. later constant	slight even fall	+++	0	slight drop	oscil-lating	0	small[1] sharp drops	+	—	——	fig. 2
136	m	26	regular with single pauses	rise and fall during first 3 min.	even and slight increase	0	++	+	0	oscil-lating	0	0	+	—	(—)	
137	m	30	irregular first 5 min. later regular	oscillating	even increase	0	++	—	0	oscil-lating	0	0	+	—	0	
138	m	45	regular	0	0	0	+	0	—	oscil-lating	0	one rather sudden drop.	++	(—)	—	
139	f	31	regular	0	even increase during whole period	0	++	0	0	oscil-lating	0	0	++	—	0	fig. 1
140	f	28	regular	decrease oscillating	even increase first 5 min. later constant	0	++	+	—	oscil-lating	oscillating increasing tendency	several sharp drops	++	—	——	
141	f	34	slightly irregular	oscillating	even increase during whole period	0	++	0	(—)	increased oscil-lating	even increase	0	++	(—)	(—)	

[1] Not noted on the figure 2.

0 = no changes +, ++, +++ = different degrees of increases. (—), —, —— = different degrees of decreases.

Ps.: 2–3 years!

ES.: He ought to have given her a hand when he realized that everything went wrong for her. Perhaps she could have pulled herself together.

Ps.: She tried to do so, but gave everything up. How do you like her?

ES.: I find that it was a poor escape to sit down and read. This does not improve matters.

Ps.: Were you able to understand her?

ES.: No! Possibly because I myself feel quite otherwise towards similar problems.

Ps.: Do you know of people who are like the woman in the story? etc.

This line of questioning and discussion was the same as that followed in the interviews with the psycho-neurotic patients, and it is likely that, if any of the topics treated had had emotional significance for the subjects, they would have reacted.

Two typical recordings during the experiments with the normal subjects are given in figures 1 and 2. The skin temperatures rose in both during the stories. The pulse rate varied more during the discussion than before. In one of the cases the skin resistance also altered somewhat during the discussion. Simultaneously with the beginning of the discussion a sharp increase in the pulse rate was found, as mentioned above. The "fright" reaction is clearly seen in both experiments, in Fig. 2 in the recording of pulse rate, skin resistance and skin temperature. A summary of the findings of all the experiments of this type is given in Table 2. Only in a few cases were any reactions greater than those at the beginning of the discussion, and during the beginning of the experiment the changes in the various recordings did not coincide. In one experiment, however, the skin resistance decreased, the skin temperature increased, and the pulse accelerated suddenly and simultaneously. Cautious checking revealed that the discussion had at this point approached some serious personal problems for the subject.

Psycho-neuroses.

A single experiment will be described in details below.

Female patient, A, 45 years, married. Her father was hot-headed and used to beat wife and children. Her mother died when she was seven years old, and her aunt took over the housekeeping. She was aware of sexual relations between her father and her aunt. Her education was characterized by lack of love and moralizing warnings against sexual relations. She married a rather shy man against her father's will. Her marriage is unharmonious, her husband is a heavy drinker and she is extremely frigid. She has 3 children. Her frigidity worries her a great deal, and she compensates for her lack of happiness by platonic loves with "husband substitutes", of whom she has had three. Her husband is jealous of these relations. Since 1949 she has been treated in the outpatient clinic of the psychiatric department of the University Hospital under the diagnosis *Psycho-neuro-*

sis on hysterical basis (confirmed by the Rorschach test). From April to December 1953 she was submitted to group therapy during which she has been considerably stabilized and has gained a more sober attitude towards her problems. She still shows hysterical reactions, but is more controlled.

January 28' 1954: The patient arrived at the laboratory at 2.10 p.m. and was placed in the experimental room ready for the experiment at 2.30. The recording devices were set going at 2.47. The recorded reactions are given in Fig. 5. Six stories were read. No. 4 was intended to have emotional content for the patient and was begun at 2.57: "*Agnes* was 5 years old, when her mother died in childbed. Her father, a blacksmith, employed a housekeeper to take care of the two children. She was in the middle of her thirties and fell in love with the big blacksmith who, however, was not inclined to marry again. Yet he was not against a little fun, and in the evening when Agnes was awake she could hear him go into the housekeeper's room. During the day he and the housekeeper used to quarrel, but the two adults always agreed about correcting and scolding Agnes (2.58). As she grew up they told her how dangerous and dreadful it was to know a man. Agnes became a pretty girl, and many of the boys were interested in her, but she did not dare to go with them, and instead she chose a shy young man who definitely would not be dangerous. Against her father's advice she married him and moved to the town. After all the marriage was a failure. Sexual intercourse was a pain to Agnes. Every time her husband insisted on having sexual relations she became rigid with fear. It did not improve matters that they could hear the couple next to their cheap little flat amusing themselves. Her husband hinted at it in order to warm her up, but the effect was the opposite. His talk of it only made her sick". (ended 2.59).

The discussion started at 3.07 and each story was discussed separately. At 3.17 the discussion of the 4th story began:

Ps.: What about the fourth story, with Agnes?

Pt.: It is completely my life, right through. It was exactly that with—I never got ... I got the impression—is this love? I thought: Is this love? It may be that it is something I ought to admire—something sweet and beautiful, but when I think of my father and my aunt, how they behaved—during the day—it is a shock for me to think that they should go to bed together. Still—I cannot get out of it what I ought to get (3.18). It is impossible for me, and therefore I have got such a—

(Impossible to hear in the recording).

Ps.: What did you feel when you heard the story? What did you think?

Pt.: I thought—I thought ...

Ps.: Just try to explain—

Pt.: I thought: It is just me. Imagine how I have been educated (pause). When one wants to get something out of it, but finds it impossible.

Ps.: Do you think that your experiences as a child made you unable to enjoy it?

Pt.: Yes—here is something. When I was a patient in the hospital and the professor was on the ward round (3.19)—then I said—yes that's it—but when one does not know how to express oneself, but I said that I got a mild shock when I was a child. Is that so, said the professor, but you must have got over it—it is long ago now. And then I thought "not even the professor can understand me", where are we now, I thought. Then I remained silent. There was nothing more to speak of—and I did not say anything further—I did not tell him anything.

Ps.: But we have talked it over in the group.

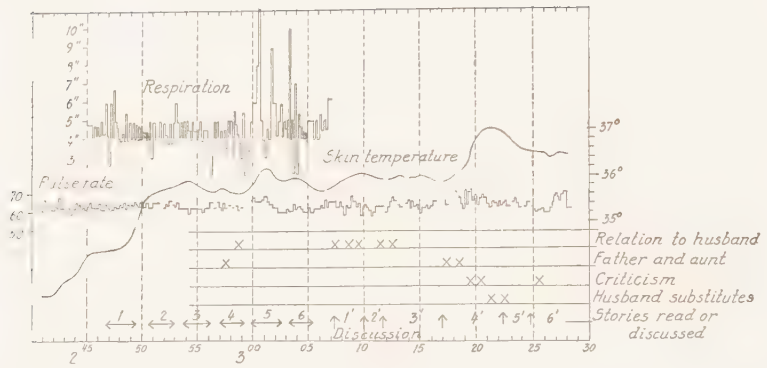

Fig. 5.

Experiment No. 122. Autonomic reaction of a psycho-neurotic patient. Tracings as in Figs. 1 and 2. The skin resistance remained constant during the whole experiment on 800,000 ohms and is not shown in the figure. Subjects with emotional content for the patient treated are indicated by crosses.

The six stories and the discussion of each story are indicated on the graph.

Pt.: Yes—I have met much more understanding there (pause). And now I keep hearing that I am childish—yes-in the way I withdraw and cannot get what I ought to. And look—I have wondered why I am childish here (3.20) I have always heard that grown-up people are so stern—and now I am 45 years old and still I am condemned—for example my girl friend, you know the one I liked so much—and visited her home so often. They always fling this at me—and say: You are childish—How childish you are. I could not figure out in what way I was childish. My friend (hints at one of the husband substitutes) tried to understand me, and help me, and explained me so many things. And I said to him after I had got to know him: "just tell me in what way I am childish. Can't you find out what it is?" He couldn't find out.

Ps.: It is your emotional reactions that are too strong. You know that children have some difficulties in controlling themselves (3.21) and you have difficulties too. You are not childish in the sense that you behave like a child. You have managed a lot of tasks marvellously—and tasks for grown-ups, etc.

As seen from figure 5, the response to the 4th story began in the pause after the story, first in the respiration, then in the pulse and some 10-20 seconds later again in the temperature.

The general discussion was preceded by a slight increase in pulse rate and temperature, the same reaction as described earlier. During the discussion of the 4th story there was a steady increase in pulse rate and temperature at the beginning, when her father and aunt were discussed, and then a very sharp rise when it was mentioned how people criticizes her. A very small, but unmistakable, decrease in skin resistance, which was otherwise constant during the whole experiment at about 800,000 ohms, was also seen during this period.

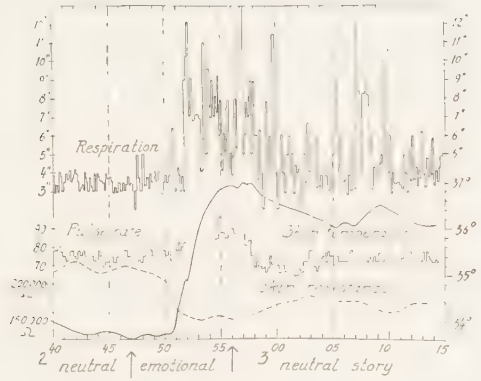

Fig. 6.

Experiment No. 112. Reactions of the psycho-neurotic patient hearing her own life history read.

Abscissa: Time in minutes.

Ordinate: As indicated.

In order to simplify the results of the experiment, the typewritten discussion was studied by a psychologist (not the interviewer) and the topics discussed from minute to minute were roughly classified, as "relations to her husband", "her father and aunt", "criticism", "husband substitutes", etc.

Fig. 6 shows the most violent reaction we have seen. It was a 26 years old unmarried female patient who was presented with her own life history, thinly disguised.

The emotional reactions of the neurotic patients are summarized in Table 3[1]. Some of the results will be presented in more details in a subsequent paper.

From Table 3 it is seen that the type of autonomic responses during emotions varies from patient to patient. For example, in patient A only a moderate reaction is seen in the pulse rate, but a conspicious one in the skin temperature. In patient C a strong reaction is seen in the pulse rate, but there are no changes whatever in the skin temperature. A reaction in skin resistance is seen in surprisingly few experiments, and it is an open question whether it is worth while to include measurements of skin resistance in experiments of this type.

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[1] The total material, including the (untranslated) unabridged interviews and stories and the original tracings is deposited in the University Library of Copenhagen.

TABLE 3

Reactions of the psycho-neurotic patients during the experiments.

Patient	Sex	Age years	Exp. No.	Date	Experimental technique	Changes in respiration	Changes in pulse rate	Changes in skin temp	Changes in skin resist	Remarks
A	f	45	122	Jan. 28' 1954	6 stories + discussion	reaction	+	++	no	(fig. 5)
			127	Febr. 11' 1954	„	no	(+)	++	no	
B	f	30	124	Febr. 2' 1954	interview	—	+	++	no	
			126	Febr. 9' 1954	6 stories + discussion	no	+	++	no	
			132[1]	March 3' 1954	„	—	m	+	no	
C	m	27	129	Febr. 19' 1954	interview	—	++	no	no	
			131	Febr. 26' 1954	6 stories + discussion	no	++	no	no	
			134[1]	March 9' 1954	„	no	+++	no	no	
D	f	45	107	Oct. 20' 1953	interview	—	?	+++	no	
			108	Oct. 22' 1953	„	—	?	++	no	

			111	Nov. 11' 1953	„	—	+	++	no	
			112	Nov. 20' 1953	3 stories, no interview or discussion	strong reaction	++	+++	drop	(fig. 6)
			113	Nov. 27' 1953	interview	—	+	++	no	
			121[1]	Jan. 22' 1954	3 stories, no discussion	no	+	+	no	
F	f	27	115	Dec. 4' 1953	interview	—	+	++	no	
			116	Dec. 8' 1953	3 stories, no discussion	reaction	+	++	no	
			118[1]	Dec. 16' 1953	„	no	+	++	no	

(+), +, ++, +++ = different degrees of increases.
— = no registration of respiration during the interview.
m = oscillating.
? = registration failed.
[1] experiment made one week after an experiment with a sedative.

The effect of repeating a situation.

It has been our experience with normal subjects that repetition of a situation causes a decrease in the reaction to it. This has been mentioned several times above. However, in general no decrease in the reactions of neurotics has been noted when the same topics have been under discussion several times. The patients responded in a similar way every time they were submitted to an interview or a story that had a personal relation to them. In a subsequent paper some curves will illustrate this. However, some exceptions were found. First, the respiratory reaction had a tendency to decrease in the subsequent experiments, whereas no decrease was seen in the pulse reaction or in the response of the skin temperature. In five cases an experiment was made about a week after the patients had been submitted to an experiment under the influence of the sedative examined. In two of these cases the responses seemed definitely lower than in the experiments before the patients were treated with the sedative; yet the reactions were higher than those seen while the patients were under treatment with the sedative. The question is still open whether this phenomenon is really due to a slow decrease of the intensity of the reactions or whether the decrease observed in these experiments is a delayed effect of the sedative used.

DISCUSSION

As could be expected, the patients responded to emotion by reactions in their autonomic system. The most consistent responses found were those of the skin temperature and the pulse rate. The reactions of the respiration and of the skin resistance were more inconsistent and absent in many cases. It is quite possible that other responses would be just as consistent, for example response in blood pressure, in cardiac output, in tension of the striped muscles, in the plethysmogram of the finger or in the oxygen saturation of the blood.

Our main conclusion is that the combination of stories and interview seem to be an excellent method for provoking and controlling emotions, especially when the aim is to repeat the situation several times in order to assess the effect of some therapeutic measure. The kind of autonomic reaction measured is of minor importance.

The reactions seen in neurotics are surprisingly small in comparison with those of normal subjects. The response of normal subjects to stress was much higher than that of patients, although the stress (e.g. the threat that a shock was to be given) was presumably smaller than the stress to which the patients were exposed (e.g. the

discussion of very personal problems). But the reactions of normal subjects have a tendency to be rapidly extinguished, in contradistinction to the reactions of the psycho-neurotics, which, if they ever show a tendency to fade, do so much more slowly. It is interesting to note that the reaction of psycho-neurotics to emotions is different in type from the fright reaction seen among normal subjects, who respond to this situation with a decrease in skin temperature of the face. We have always found an increase of skin temperature when the psycho-neurotics have been exposed to emotional stress during the discussion of their personal problems. The psycho-physiological importance of this phenomenon should be underlined, but a further examination of it was beyond the scope of the present investigation.

SUMMARY

Seven normal subjects and six psycho-neurotic patients have been submitted to a verbal stimulus under which emotions were provoked. During the experiments, respiration, skin resistance of the palm, skin temperature of the face and pulse rate have been recorded. The normal range of variations during neutral periods is described. The subjects of both groups responded with clear changes in the autonomic mechanisms measured. The responses of the normal subjects were in general more pronounced than those of the psycho-neurotics, but showed a definite tendency to be extinguished when the situation was repeated, whereas the reactions of the psycho-neurotics could be provoked with almost the same intensity in several experiments one after another. The technique described can be utilized for evaluating the effect of therapeutic measures.

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FROM THE BIOLOGICAL LABORATORIES OF MEDICINALCO, LTD. (ERIK JACOBSEN, M.D.) AND THE UNIVERSITY CLINIC OF PSYCHIATRY, RIGS-HOSPITALET (PROFESSOR VILLARS LUNN), COPENHAGEN, DENMARK

THE AUTONOMIC REACTION OF PSYCHO-NEUROTICS TO A NEW SEDATIVE: BENACTYZINE NFN, SUAVITIL (R) (BENZILIC ACID DIETHYLAMINOETHYLESTER HYDROCHLORIDE)[1]

By

ERIK JACOBSEN, HELLE KEHLET, VALDEMAR LARSEN,

IB MUNKVAD and KIRSTEN SKINHØJ

The effect of drug therapy on psycho-neurosis is extremely difficult to evaluate. The course is unpredictable and depends not only on the treatment, but also on factors entirely outside the therapist's control, as for example, changes in environment. Moreover, the evaluation of results generally must be based on the patients' subjective statements. Therefore, examination of the effect of a single therapeutic measure, in this instance treatment with a drug, can be done only in two possible ways. Either the drug can be given over a long period to patients in a fairly stable phase of their disease, and the results can be assessed from the patients' or their relatives' statement about an improvement or its absence, or it may be possible to find objective tests by which to measure the patients' reactions to situations similar to those affecting them in daily life. The patients are submitted to such tests before, during and after administration of the drug under investigation. Each method has its advantages and disadvantages. The second method does not necessarily involve the patient's cure or any feeling of subjective improvement during medication as the changes are measured by objective methods; a shorter observation time suffices, but the method is laborious. The first method requires a long observation time, carefully selected patients and a very cautious judgment of

[1] In some countries this drug is marketed under the name of Parasan.

the patients' subjective statements. Needless to say, in both methods due consideration must be given to the powerful influence of suggestion in psycho-neurosis.

By experiments on animals and human subjects a certain compound has been found to have a specific sedative effect on the central nervous system. This compound is *benzilic acid diethylaminoethylester hydrochloride* ($(C_6H_5)_2COHCOOCH_2CH_2N(C_2H_5)_2$, HCl) (*Suavitil* (R) Benactyzine NFN). It is anticholinergic corresponding to ¼ of atropine measured on the isolated guinea pig's intestine. The effect on the central nervous system seems to be rather specific. After 5–10 mg a human subject subjectively feels a blocking of the thoughts, heaviness of the limbs, objectively the α-waves in the EEG disappear. When given to cats or rats under mental stress it normalizes the behaviour of the animals (*Jacobsen and Skaarup*, 1955; *Jacobsen and Sonne*, 1955). It is without hypnotic effect used on humans or animals in any dosis. A clinical effect is seen with doses not giving any other subjective or objective symptoms.

Preliminary investigations of this new type of sedative indicated a sufficiently good effect on psycho-neurotics to warrant further investigation. Both methods mentioned above have been used in this investigation. The results of the clinical experiments of long duration are being reported by *Munkvad* (1955). The present paper describes the results of experiments of the second type.

TECHNIQUE

The patients examined were all attending the Outpatient Clinic of the Psychiatric Department of the University Hospital, Copenhagen. In a series of experiments emotions were induced in the patients while their autonomic reactions were measured. The details of the technique the normal reactions and have been described in an earlier paper by *Jacobsen, Kehlet, Larsen, Munkvad* and *Skinhoj* (1955) and will not be given here.

Some preliminary orientating experiments are also left out here. In the later experiments the following method was used: Patients were examined once or twice, some times after the administration of placebo tablets. Thereafter, they were treated with Suavitil tablets for one week and then re-tested under the same conditions as before. The medication in general was as follows:

1st and 2nd day 0.5 mg 3 times daily
3rd to 5th day 1.0 mg 3 times daily
6th and 7th day 1.5 mg 3 times daily

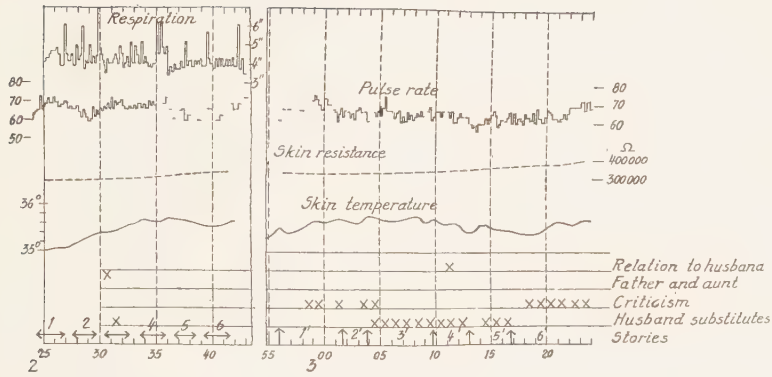

Fig. 1.

Complete tracing of experiment No. 125, patient A, after one weeks' Suavitil treatment.

Abscissa: Time.

Ordinate: Duration of each respiration, pulse rate per minute, skin resistance in the palm, skin temperature (Centigrades). The topics discussed from minute to minute are indicated by crosses. The patient had been pretreated with Suavitil during one week, as indicated in the text. After the stories, the experiment was interrupted for 12 minutes because the tape-recorder failed.

Placebo tablets were then given for another week, and the patients were submitted to final tests. No side effects were reported during this medication.

RESULTS

Patient A: The case history and the result of the first experiment are given in the text and in fig. 5 of the previous paper (*Jacobsen et al.* 1955). After this experiment on January 28' 1954, the patient was given Suavitil as indicated above.

She had been well balanced during the week. She arrived at the laboratory at 1.50 p.m. on Feb. 4th and immediately received 1.5 mg Suavitil. The test began at 2.23 p.m. The autonomic reactions are given in Fig. 1. Six stories were read, different from the stories read in the first experiment. No. 3 had an emotional content for the patient. Abridged it sounded:

"Dora was unhappy in her marriage. She and her husband did not get on very well together. During a holiday she met Jensen. They had long walks together, and she had the feeling that he understood her much better than her husband did. After her holiday she phoned Jensen and they met again. He too was married, and his wife was extremely jealous. They would have continued their friendship, but the relation was too heavy a load for both, and finally they agreed that they would not meet again."

The discussion about this story began at 3.04'30" and sounded:

Ps.: What about the next story, about Dora who was unhappy in her marriage?

Pt.: That's again my own story. Almost the same thing has happened to me. I can remember that it hurt me very much (3.05). I told the story to a psychiatrist,

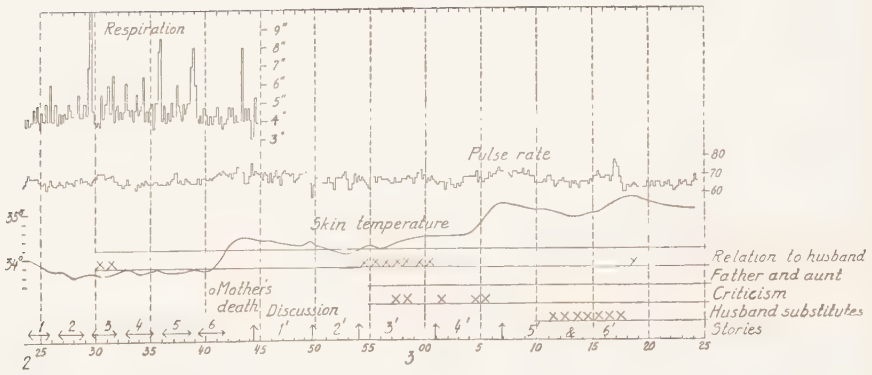

Fig. 2.

Complete tracing of experiment No. 127 made a week after experiment No. 125, patient A. Legend as in Fig. 1. The patient took placebo tablets during the preceding week.

but he said that I easily fell in love. I think of my sister and many others who cannot get on a tram without trying to flirt. It hurt me very much. I took it as a reproach and thought: "No, I have never done that." When I now think about the whole thing, I find that it was peculiar how everything happened.

Ps.: What was peculiar? That you fell in love with him all the same?

Pt.: Yes, yes, no, I do not think there is anything peculiar in that, but I mean that it was far from that I was trying to flirt or, as you know, anything else. Yes, try and try, I do not know. It happened like this, you see. We were placed at the same table and then ... (3.06). One can see if a fellow man is miserable and is in trouble, one can almost see then, and when you then speak to them you learn why they are miserable, and then ... I had almost said it was as if ... yes you cannot help it that you are going to love such people.

Ps.: Do you think that you did something wrong when you loved him?

Pt.: No, I did not think so, I thought ... If there ... I thought that for me it is the purest of the pure (3.07). So it looks to me.

Ps.: Did he kiss you or did he make advances?

Pt.: Yes, but I did not feel it as such. It was most natural, I found. I find that it is as if—yes, I don't know. Yes—I can tell myself, I can tell myself—Yes—"If you had been strong enough to keep him at a distance and and so—Then it would not have happened, but it did not go that way.

Ps.: Did you have sexual intercourse with him?

Pt.: No.

Ps.: Did you feel like it, then? (3.08) (the continuation is abridged).

Pt.: I felt that it was natural, as it ought to be. Yet at the last moment I refused. I think it was the influence of religion. He also believes in God. But he was unhappy, and I want to try to help him. I am for example tempted to go and talk to his physician. But it is better not (3.09). When I phone him I can hear from his voice how glad he is.

After the test her Suavitil bottle was changed for a similar bottle containing dummy tablets, of the same size and taste.—She was asked to continue taking 3 tablets daily,, and to return to the laboratory a week later. When she arrived on Feb. 11, she stated that she had felt very miserable during the preceding week.

She complained of hot flushes and sleepiness "after the tablets". Furthermore she had learned, on the day before the 2nd test (whilst she was still on Suavitil) that a husband substitute had died. She did not mention this on February 4th or show any grief. However, during the week where she was on dummy tablets she was full of grief and mentioned the topic as soon as she arrived for the 3rd test.

She arrived at the laboratory for the 3rd test at 2 p.m. and was given 3 placebo tablets. The experiment No. 127 began at 2.23. The reactions are given in Fig. 2. Six stories were read, different from the others. Story No. 3 was meant to have an emotional content it was about a wife with an alcoholic husband. The story No. 6 was meant to have emotional content for another patient: A mother was very good to her children but died. Her husband was economically badly off and went bankrupt.—During the discussion of the 4th story she said about a girl friend. 3.05: (abridged) "She did not like my husband, we had been friends before I married. When my husband went bankrupt (3.06) I told her that I was going to sell all my things, but she said that this was silly. She is very fond of clothes and so on. I thought she was right and did not sell anything; after all, my husband would spend the money on drink."

3.14'30" (during the discussion of the friend's death): "It was decidedly the best for him, but it is difficult for his wife to be left with 3 children.—When I compare this with my own affairs (3.15) I feel that it is also difficult for me, and I almost wish that I had died instead of him." (3.16)

Ps.: The matters we talked about the last time, have they caused you any speculation? (3.16'30")

Pt.: Better to be honest; when I went from you last time I went to see A (the husband substitute discussed last time). I have compared my worries with his (3.17). It seems as though everything goes better with me and worse with him. I feel that he suffers very much (3.17'30").

The results of these tests will be discussed later in connection with the other results.

In the following no detailed curves will be given, but only the parts of interest in demonstrating the effects.

Patient B: Housewife, 30 years old. She grew up under modest circumstances. Her mother was often ill and died when the patient was 14. She felt herself more linked to her father, but has later realized that her mother was the person who kept the home together. From her 16th year when she left school, she had several domestic posts. She entered the school for Art and Industry, but was rather lazy and left after a short time. She married when she was 21. She has 3 children, one born before her marriage, of one of several possible fathers, and adopted by a childless couple, and two since her marriage. Her marriage is not too happy, she finds her husband stern and reproachful. She has complained of depressions, and reproaches herself that she is aggressive, irritable, lazy and stupid. She also overeats, especially when she is depressed. She has been attending for group therapy from October to December 1953 at the Outpatient Clinic of the Psychiatric Department of the University Hospital, Copenhagen.

Experiment No. 124: February 2' 1954 (Fig. 3). Interview with rapidly changing topics. The pulse rate was rather labile, and it was not always possible to find connections between the topics discussed and changes in the pulse curve, but

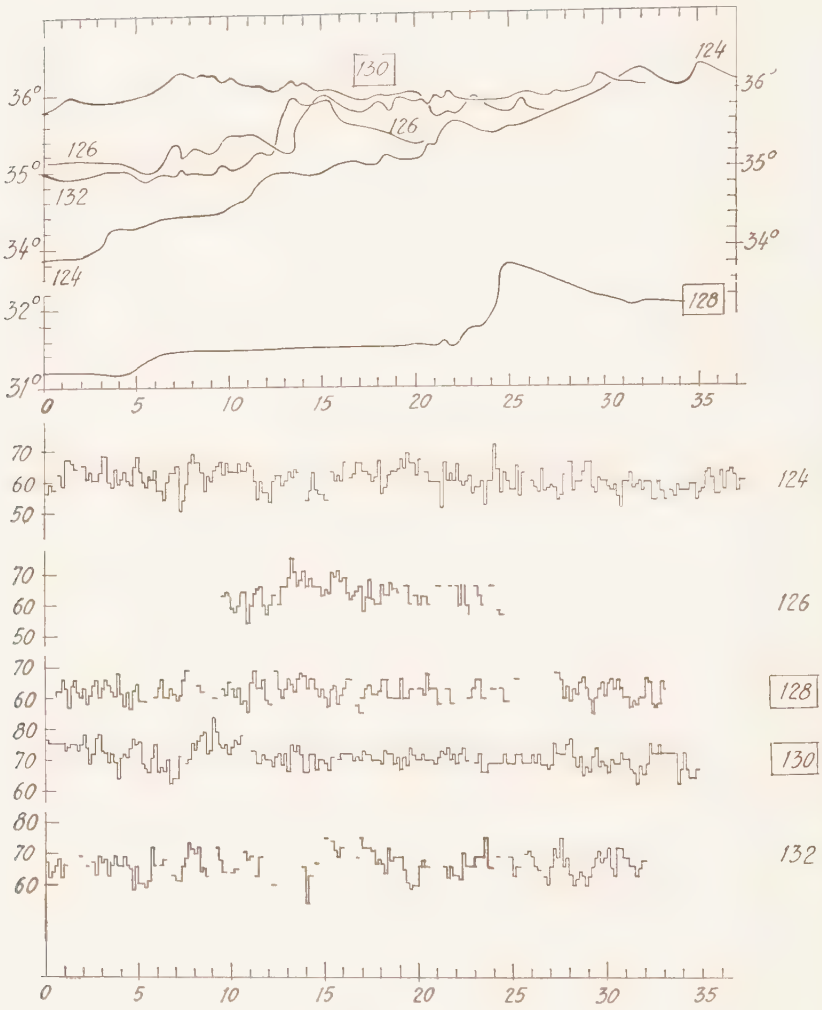

Fig. 3.

Recordings of skin temperature and pulse rate in the experiments on patient B. Only the last part of the recordings have been given and the reactions to the stories are not indicated.

Ordinate: Skin temperature (Centigrades) and pulse rate in beats per minute.

Abscissa: Time in minutes.

Zero time in the graph corresponds to the 30th minute of experiment No. 124, the 26th minute of experiment No. 126, the 25th minute of experiment No. 128, the 25th minute of experiment No. 130, and the 35th minute of experiment No. 132.

Experiment No. 124 and No. 126 were made without premedication.

No. *128* after 1.0 mg Suavitil 3 times daily for one week.

No. *130* after 1.5 mg Suavitil 3 times daily for one week.

No. 132 after 3 placebo tablets 3 times daily for one week.

The recording of the pulse rate failed partially in experiment No. 126.

there were fairly regular responses when her childhood, her mother's death and her relations to her father are mentioned. The skin temperature increased during the whole experiment with steep rises when the talk was about her mother's death, $> 1°$ in less than 15 sec. (not shown in the figures), and when she related how an uncle told her father about her illegitimate child (4' minute of the graph).

Experiment No. 126: February 9th 1954 (Fig. 3). 6 stories and interview. The skin temperature stabilized during the 3rd story. During the 4th story with emotional content, a response in the pulse and a clear alteration in the respiration was seen; immediately after the story a sharp rise in the skin temperature of the same type as in patient A appeared. (Not shown in the figure).

During the discussion the patient acknowledged that the 4th story concerned her. She was reproaching herself bitterly at a time corresponding to the 12th minute on the graph scale. During this period of strong emotional pressure the patient wept and sharp increases in pulse rate and skin temperature was seen.

Experiment No. 128: February 16' 1954 (Fig. 3). The patient was then given Suavitil 1 mg 3 times daily until February 16', when she took 1 mg in the morning and 1.5 mg at 10 a.m., half an hour before the beginning of the experiment. 6 stories were read, different from those in experiment No. 126. The emotionally loaded story (No. 3) was based on the patient's childhood and her mother's death.

During the 3rd story no real increase in the skin temperature was seen (not given in Fig. 3), but the pulse increased though rather slowly. A weak reaction of the pulse was seen when the discussion began (not given in Fig. 3). The rise in skin temperature at about the 5th minute was not accompanied by any increase in pulse rate and the discussion at that time was adjudged emotionally neutral. No apparent reactions in the pulse rate or in the skin temperature was seen during the discussion of the emotionally loaded story, but the emotional pressure exerted by the experimentalist was rather small and she avoided talking about the points that earlier had given autonomic responses. At about the 20th minute in the graph she stated that she had difficulties in keeping to a train of thoughts.

The discussion went on to the 5' story, about a spoiled boy, who later in life lacked in self-confidence and became irritable and hot-tempered. The patient here explained that she also is lacking self-confidence and is lazy (22' min.), and that she tries to escape from reality by reading exciting magazine stories (23' min.). She has a bad conscience, but lacks the energy to do her housekeeping (24' min.). She finds life dull, but she has to work, and there is a great deal to do in the house (25' min.). During this period a sharp increase in the skin temperature was seen, accompanied by an increase in the pulse rate 2 minutes later. During the whole experiment no change was seen in the skin resistance.

Experiment No. 130: February 24' 1954 (Fig. 3). The following week the patient took 1.5 mg Suavitil 3 times daily. On Feb. 24 she was given 1.5 mg in the morning and 2 mgs half an hour before the experiment began.

6 stories were read, the second was about a girl who was unhappy, who got an illegitimate child and tried to console herself in her unhappiness by eating. During the stories an even rise was seen in the skin temperature from about 32° to 36°. No change was seen in the pulse rate during this period. The second story was discussed at some length from 3' to 17' min. on the graph. She recognized her own history during the discussion. She was full of self-reproach and wept a little from the 7th to 9th min. Before the weeping there was an increase in skin temperature and a minute later in the pulse rate. The discussion of the same topics was continued during the following minutes with the same emotional pressure, but

both the pulse rate and the skin temperature decreased, the latter with minor undulations. During the discussion of the third story about an office girl who flirts with her employer, she stated that she is too fat and nobody, not even her own husband, cares for her; it is more than a week since he has kissed her. She sobbed a little (22'–23' min.), but no reaction was seen except perhaps a slight increase in the pulse rate. The last emotional passage was from 27' min. when the talk was about a young man with lack of self-confidence; this was accompanied by a slight increase in the pulse curve.

Experiment No. 132: March 3' 1954. (Fig. 3). The following week the patient was given 3 placebo tablets 3 times daily.

Half an hour before the experiment she was given 4 placebo tablets. This time the 4th story was emotionally loaded; it was about a housewife who could not get through her work in the house and with her children. An increase in the skin temperature was seen after the 1st, 2nd, 3rd, during and after the 4th, and slightly after the 5th story, the latter followed by a reaction in the pulse rate. The pulse rate increased just at the beginning of the discussion and the same was seen with the skin temperature. There were several earlier minor reactions. During the discussion about the 4th story, when the patient was asked what she felt when she heard it, she stated—with long pauses and much sobbing that she found herself useless, and her task hopeless. The autonomic responses were here on the 13th-14th min. on the graph very clear and sharp. The psychologist broke suddenly from the theme (15th min.) and began to talk about the patient's interests.

Patient C: Male worker, 27 years old (Fig. 4). He grew up in very unharmonious circumstances. His father drank and was extremely brutal. He lived at home until he was 19 and then married a young girl whom he had known since he was 16. He had a talent for painting and has tried to make a living out of his art, but so far in vain. He feels tied to his mother and has, since his boyhood, tried to protect her against the brutality of his father, whom he strongly dislikes. In his marriage, which as a whole is very happy, he is extremely jealous and has several times attacked and fought supposed rivals.

During recent years he has developed anxiety, to begin with rather diffuse. Lately he has been afraid of failure, thought he had cancer and that he would die of heart trouble etc. He felt restless and complained of lack of concentration. He has not been treated by group therapy and was not known in advance by the psychologist.

Experiment No. 129: February 19th 1954. (Fig. 4). Interview. Only the pulse rate responded, but here violent responses were seen when his relations with his father and his jealousy were discussed.

Experiment No. 131: February 26' 1954. (Fig. 4). 6 stories. No. 4 was emotionally loaded. He responded as in the earlier experiment to talk about his parents and his rivals. (e.g. the 10th, 14th, and 20th minute in the graph).

Experiment No. 133: March 4' 1954. (Fig. 4). From Feb. 27th to March 3rd he was given 1 mg Suavitil 3 times daily. On March 4th he took two doses and was given 1.5 mg half an hour before the experiment.

6 stories were read. The 5th story about a young wife's infidelity produced a sharp increase in the pulse rate (up to 95 beats per min. not shown on the graph). The increase seen on the graph about 5'–7' min. accompanied some inexplicable bursts of laughter (also seen in other persons under the influence of Suavitil). He stated that he had some difficulties in following the stories and felt sleepy. The

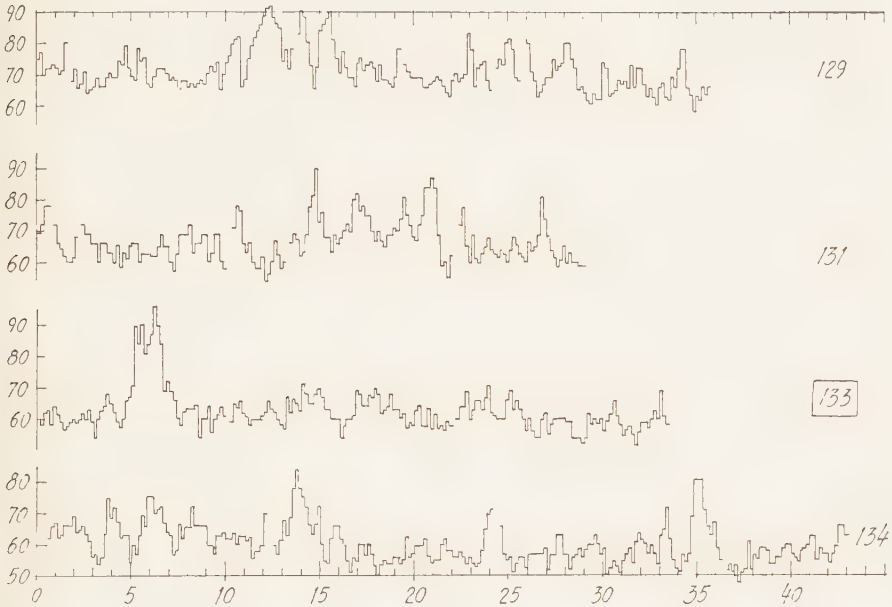

Fig. 4.

Partial recordings of pulse rate in the experiments on patient C.
Ordinate: Pulse rate in beats per minute.
Abscissa: Time in minutes.
Zero time in the graph indicates: 22th min. of experiment No. 129
25th min. of experiment No. 131
20th min. of experiment No. 133
23th min. of experiment No. 134
Experiment No. 129 and 131 made without premedication.
133 after 1 mg Suavitil 3 times daily for one week.
134 after 2 placebo tablets 3 times daily for one week.

discussion of the emotionally loaded story was very characteristic for patients treated with Suavitil:

Pt.: Yes, you do not need to tell that story again.

Ps.: What were your thoughts when you were listening? (13' min. on the graph) (pause).

Pt.: I thought about so much (pause).

Ps.: Things you don't want to speak about?

Pt.: Honestly no. Not today, in any case (pause).

Ps.: Do you find it impressed you more today than it would do another day?

Pt.: I think so—because this story, and the story last time were very close. I cannot help it. They are extremely well written.

Ps.: Do you think they are similar to your own problems?

Pt.: Absolutely (14' min.). They could not be closer.

Ps.: Do you think that you get wiser when you listen to your problems in this manner?

Pt.: Wiser?

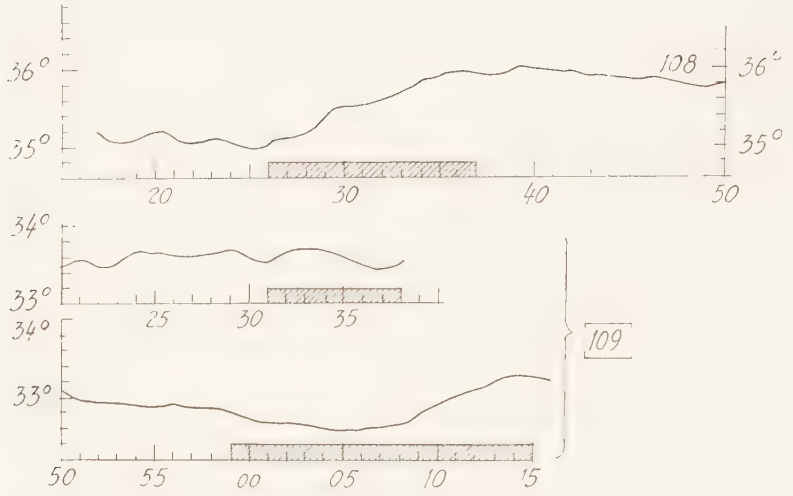

Fig. 5.

Partial recordings of the reactions of the skin temperature of patient D.
Ordinate: Skin temperature (Centigrade).
Abscissa: Time in minutes.
The top tracing from experiment No. 108. The lower tracings from experiment No. *109* after one week's treatment with Suavitil (1.5 mg 3 times daily).
The blocks indicate the time during which relations with her female friends were discussed.

Ps.: Yes.

Pt.: Not today in any case.

Ps.: Do you not find that you can place yourself in a position from which you can see everything from outside?

(inaudible recording).

Pt.: And I got extremely angry.

Ps.: Why?

Pt.: Why -etc. (14¾ min.).

The patient apparently avoids discussing the problem, and the discussion continued about various ways of abreacting.

Experiment No. 134: March 9' 1954. (Fig. 4). The patient was then given placebo tablets during the following week.

The experiment began with 6 stories as in the earlier experiments, the 5th being emotionally loaded. The reactions in this experiment were characterized by several sharp rises in the pulse rate when emotional problems were discussed.

Patient D: Housewife, 45 years. She appeared immature with inferiority feelings and was sensitive and labile. She felt uncertain in heterosexual contacts, generally indifferent, but she showed a definite distaste for masculine genitalia or their symbols. She was inclined to establish strong links with dominating women and in such relationships was extremely vulnerable and ready to react with jealousy. She was too inhibited to abreact, but directed her aggression inwards and developed somatic symptoms with depressive reactions.

Three experiments were made with her, two of which are partly shown in Fig. 5. In all the experiments she was submitted to interviews only. The first experiment

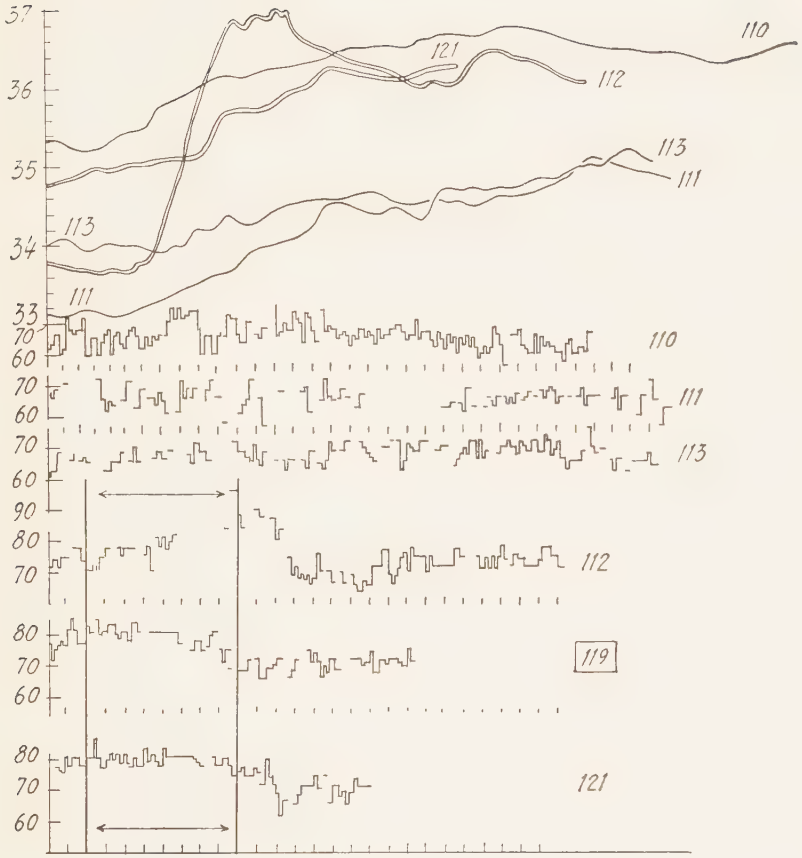

Fig. 6.

Partial recordings of the skin temperature and pulse rate of patient E. Experiments 110, 111, 113, and 121 without premedication. Experiment *119* with the premedication, 1.5 mg Suavitil 3 times daily for one week. Experiments 110, 111, and 113 were made only with interviews. Experiments 112, *119,* and 121 only with stories, indicated by arrows. The temperature reactions during experiments 112 and 121 are drawn with double lines. The recording of the skin temperature failed during most parts of experiments *119*, but reliable measurements immediately before the listening to the emotional story showed 32°, and immediately after 32.6°.

(not shown on the graph) was made with rapidly changing themes, in the others each theme was discussed for longer periods. She reacted when authorities (father, former employers) were discussed, but especially when she was interviewed about her relations to female friends. (Fig. 5). In the last experiment (No. 109) Suavitil has been given during the preceding week (1.5 mg 3 times daily). It was seen that the relation to her female friends could now be discussed for several minutes with no reaction in the skin temperature. Only after hard pressure, during which she was asked about possible bodily homosexual relations which she never has had, (31'–37' and 59'–15' in experiment No. 109), was a delayed, but distinct reaction seen in the skin temperature.

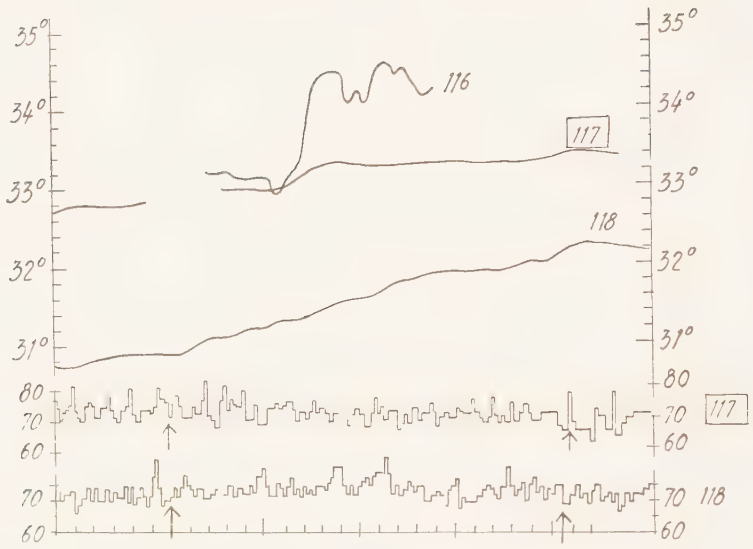

Fig. 7.

Partial recordings of the reactions in skin temperature and the pulse rate of patient F. In experiments Nos. *117* and 118 the patient's letters were read, the beginning and the end being indicated by arrows. Experiment No. 116 was made with the interview technique and shows the responses at a higher skin temperature than in experiment *117* on a topic similar to that mentioned at the same time in the letters. Before experiment No. *117* 1.5 mg Suavitil was given 3 times daily for one week. Experiment No. 118 was preceded by 5 days of placebo medication.

Patient E: Female worker, unmarried, 26 years old. She had a rather unhappy childhood with a stepfather who according to her several times tried to assault her sexually. Her mother was stern and severe and lacked understanding. She is jealous of her mother. She had developed a deep fear of all sexual matters, menstruation, pregnancy and sexual relationship. Being engaged, she several times attempted to combate this fear, but with little success. As a result she felt anxious, tired and depressed. Moreover, she suffered from obsessive thoughts; for example she felt inclined to throttle her landlady who reminded her of her mother.

She took part in six experiments (Fig. 6), the first two exclusively with interviews, the third with long stories without interview, the fourth with an interview and the two last with long stories without interviews. The neutral stories were different in all the experiments, but she was three times presented with the same emotionally loaded story, based on her own life. During the experiments she reacted to recollections of sexual experiences in her childhood and as an adult, and to mentioning of her obsessive thoughts. The first time she heard her own story she developed the most violent reaction we had ever seen (Fig. 6 in the preceding paper). When the story was repeated while she was under the influence of Suavitil, her reaction was much less. She recognized the story, but declared that something must have been altered since she heard it the first time. When she was made to hear the story for the third time without Suavitil she reacted again, not so violently as when she heard it for the first time, but a little more than when under influence of Suavitil.

Patient F: Housewife, 27 years. Four experiments were made with this patient, one with interview, and 3 with long stories without discussion. In the third experiment (No. 117) after one week's treatment with Suavitil some letters earlier written by her to the psychologist describing her problems were read aloud. In the last experiment after 5 days on placebo tablets (No. 118) the same letters were read again. The results are given in Fig. 7.

DISCUSSION

It was hoped that clear results could be obtained in one or two experiments. The first patients were submitted to an interview lasting about half an hour; thereafter an injection of Suavitil or saline was given and the experiment was continued. However, this technique did not lead to the desired result, firstly because as the clinical experiments showed medication over some days was generally necessary to give a clear sedative effect, secondly because it was difficult to estimate the proper dose. For this reason the technique described above was adopted.

In general, responses of the autonomic system were less pronounced when the patient was under the influence of Suavitil than without premedication, or on dummy tablets.

In patient A the skin temperature was definitely more constant during the experiment with Suavitil than either before or after (Fig. 5 in the preceding paper, and Fig. 1 and 2 in this paper). Pulse reactions were found in the Suavitil experiment, but less pronounced than in the two control experiments. The discussion of the patients' own story was followed by an increase of the pulse rate, but this did not continue in spite of the prolonged emotional pressure (3.06–3.09 Fig. 1) described in the text. During experiment No. 127 (Fig. 2, 3.14–3.17) the reaction was again more pronounced than during the discussion of the same topic in the Suavitil experiment.

The results of the experiments with patient B (Fig. 3) were less pronounced than the results with patient A. The skin temperature appeared steadier in the Suavitil experiments (128, 130) than in the control experiments with exception of the single steep increase in exp. 128. However, the skin temperature in experiment No. 130 was so high that much further rise could not be expected. Except for the broad response from the 7th to the 10th minute of the graph Fig. 3 in curve 130 the pulse curves were more stable when the patient was under the influence of Suavitil than before. In the last control experiment (132) the reactions were again much more pronounced.

The results of patient C were similar (Fig. 4). In the Suavitil experiment (133) he responded with an increased pulse rate to the emotionally loaded story, which is not shown on the graph. The increase

seen in the 5th minute of the graph Fig. 4 (133) was connected with laughter. Apart from these two reactions the curve is much more stable than those of the experiments without Suavitil.

With patient D emotionally loaded topics could be discussed for a much longer time without any reaction when the patient was under the influence of Suavitil than in the control experiments. She first began to react when direct homosexual approaches were mentioned, a much stronger pressure than was applied in the control experiment.

In patient E (Fig. 6) unfortunately, the registration of the skin temperature failed during the emotionally loaded story in the Suavitil experiment (curve 119) but in any event the skin temperature was found to be very low in this experiment and increased only 0.6° during the story. There was no pulse reaction to the emotional story in this experiment; on the contrary, the pulse rate began to decrease during the period when the emotional reactions were seen in the other two experiments with the same story. In the subsequent control experiment (curve 121) no reaction was seen in the pulse rate, and a decrease appeared first towards the very end of the emotional story. However, the skin temperature increased markedly.

From the experiment with patient F (Fig. 7) it can be seen that, apart from a single short sharp rise, the skin temperature was far more constant in the Suavitil experiment (117) than in the control experiments (116 and 118). The pulse rate was steadily decreasing during the whole "emotional" period, and no reactions were seen in the Suavitil experiment (117). At least two clear responses at the 9th and 11th minute after the beginning of the letters, were found in the following control experiment (118) in which the patient was exposed to exactly the same letters as in the Suavitil experiment.

In general the patients A, C, D, and F clearly show less reaction under the influence of Suavitil than without. In the patients B and E the differences were less pronounced, but the tendency was the same.

If the diminished reactions during the Suavitil experiments are to be ascribed to the effect of the drug, the emotional pressure during the Suavitil experiments must have been at least equal to the emotional pressure during the control experiments. A careful study of the recordings actually shows that the pressure from the psychologist probably must have been the same, and often even higher, during the Suavitil experiments. The fragments of the discussion with patient A given in the preceding paper and in this one show this. Moreover, the psychologist was requested from the control room to press harder when the expected reactions to a given topic were absent. In some of the experiments the patients sometimes tried to avoid their problems,

while under the influence of the drug, in spite of the pressure from the psychologist; an example of this is given in the part of the discussion with patient C in experiment No. 133.

In two of the patients (E and F) the autonomic responses in the control experiments made after the Suavitil experiment was less pronounced than in the control experiments before Suavitil although in both they were more pronounced than during the Suavitil experiments. This seems to be in contradiction to the fact that the patients generally showed no decline in the reactions during several experiments without Suavitil. However, the patients were both exposed to exactly the same situation as during the Suavitil experiments. One possibility is that the repetition of exactly the same stimulus causes a weaker reaction in general. An alternative explanation is that the patients have been able to abreact the situation while under the influence of Suavitil in such a way that a repetition of the situation made little impression the third time.

Two of the patients (A and C) declared spontaneously that they had been less troubled during the week in which they received Suavitil tablets. Patient D has continued taking 1.5 mg Suavitil 3 times daily for more than 9 months and declares that she cannot be without its sedative effect.

On the whole it may be concluded that the drug tested has caused the patients to show less reaction to emotional stimuli than when without premedication. In some of the patients no reactions at all was seen. In others the emotional pressure had to be more severe and more prolonged (e.g. patient D) in order to provoke them. This conforms well with the observations made on rats (*Jacobsen* and *Sonne* 1955). These experiments clearly show that more intense stimuli are able to break the "Suavitil barrier" and cause the same reactions as are seen in the control experiments without Suavitil. The same was also seen in the clinical experiments (*Munkvad* 1955). The patients treated with Suavitil were able to meet the daily stress of life better, but they still felt nervous when something unexpected or more complicated happened.

The technique applied permits one to see objectively effects on the experimental subjects. It is still an open question whether the registered effect is due merely to a blocking of the autonomic centres in the central nervous system or to an influence at a higher level. The trend on the part of the patients to avoid painful discussion suggests the latter.

Finally it is clear that the variations, both from patient to patient and from experiment to experiment with the same person, are too great

to demonstrate anything more than an effect of the drug. For this reason, and because experiments of this type are very laborious, the method described cannot be used as a screening test for a series of drugs. Nevertheless—by such experiments in combination with others —we may be able to obtain important information in the field of psychopharmacology.

SUMMARY

In experiments with 6 psycho-neurotics exposed to an emotion-provoking stress it was shown that the autonomic responses to emotion were less when the patients were under the influence of a sedative of a new type (Benzilic acid diethylaminoethylester. HCl = Suavitil (R) = Benactyzine NFN).

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FROM THE ST. HANS HOSPITAL, DEPARTMENT D, ROSKILDE, DENMARK
(ARILD FAURBYE, M.D.)

CHLORPROMAZINE ("LARGACTIL") IN THE MANAGEMENT OF PSYCHOTIC PATIENTS[1]

By

SVEN MUNCH-PETERSEN

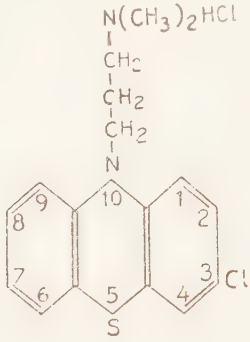
As in other mental hospitals, excited and noisy patients have presented a great problem to us. The available armamentarium— various sedatives, occupational therapy, E.C.T., insulin therapy, and lobotomy —is still so incomplete that failures are common. Any remedy which appears to have a sedative effect must therefore be utilized and thoroughly tested in an attempt to determine its range of indications.

About one year ago, our attention was drawn to 4560 R.P. listed by W.H.O. as chlorpromazine-hydrochloride and marketed by May & Baker under the name of "Largactil". In this country, the remedy is so new that any experience based on systematic testing is bound to be received with interest.

Chlorpromazine (hereinafter called C) is a phenothiazine derivative, viz. 3-chloro-10(3'-dimethylamino-n-propyl) phenothiazine hydrochloride. It is chemically related to the indicator methylene blue and closely related to a number of phenothiazine derivatives used in clinical practice, amongst others phenergan (promethazine), but almost without the antihistaminic effect of the latter. C. is a faintly yellowish white crystalline powder with a slightly pungent smell. It is freely soluble in water (at the ratio 1 to 2.5). In the aqueous solutions used, the pH ranges from 4 to 5, being thus shifted to the acid side. Apart from the acid reaction, the substance is also reported to be irritating to the tissues. Light may stain the solution, which therefore should be stored in a dark place, although the stained solution does not appear to exert a less potent effect. The drug was first produced in the Rhône-

[1] Paper read before the Danish Psychiatric Society on Nov. 20, 1954; with a few additions.

Poulenc laboratories, and comprehensive animal experiments as well as the first clinical trials were performed in France.



PREVIOUS EXPERIENCE WITH CHLORPROMAZINE IN ANIMAL EXPERIMENTS

The thorough experiments of *Simone Courvoisier* and her associates (1952) (6) on dogs, rabbits, rats, and mice will be briefly reviewed, as the results apply in all essentials also to humans. The average fatal dose was 75 mg/kg by mouth. Intramuscular administration was not used. Death occurred after loss of muscle tone followed by convulsions and respiratory failure. The rate at which death ensued varied from species to species. Histological examination post mortem showed only slight dilatation and congestion of the glomeruli and convoluted tubules. Similar, but less marked, changes were observed following subcutaneous administration of moderate doses to dogs over a period of one month. Following oral administration the renal changes were even less marked. No changes were observed in other organs. The absorption and excretion of C. have not been sufficiently elucidated owing to difficulties in determining C. in biological fluids. The commonest method appears to be red staining by oxidation with sulphuric acid. Upon administration of doses of up to ¼ mg/kg to rabbits, it has been demonstrated that C. is easily absorbed from the digestive tract, but that only a few per cent are demonstrable in the blood or urine at the end of 3 hours. The breakdown must therefore be presumed to be rapid. Schematically, the effect of C. in animal experiments may be divided into a predominantly peripheral and a predominantly central effect. The former may be subdivided into predominantly sympathicolytic and faintly parasympathicolytic. The sympathicolytic effect is apparent from the fact that C. counteracts the hypertensive effect of epinephrine and its other actions except for hyperglycæmia. The faintly parasympathicolytic properties manifest themselves in counteracting the bradycardia, hydrochloric acid secretion, and intestinal contractions caused by acetylcholine. In animal experiments, the administration of C. in doses of the magnitude used in clinical practice exerts, despite a faintly vasodilatory effect, practically no action upon blood pressure or pulse rate. Higher doses, however, result in bradycardia owing to delayed conduction and at times in bundle branch block. In clinical practice, on the other hand, tachycardia and hypotension are common findings. In animal experiments respiration remains unaffected and so does the renal function, whereas in clinical practice polyuria is common. Among the so-called central effects of C. in animal experiments, it is worth mentioning

its depressive effect upon artificially induced fever. Thermoregulation is suppressed, homothermic animals being transformed into poikilothermic. This effect has seldom been observed in clinical practice. The oxygen uptake by nerve cells from the guinea-pig brain is distinctly reduced, whereas the metabolic rate of the rat is only temporarily lowered. In man, the metabolic rate has usually proved to be lowered. This was not, however, confirmed by *Lehmann & Hanrahan* (1954) (13). In the rat conditioned reflexes are inhibited. Apomorphine-induced vomiting is blocked. In animals, C. counteracts certain convulsivants, but not others, and the preparedness for convulsion following treatment with C. is a disputed clinical problem. C. potentiates the effect of anæsthetics, hypnotics, and analgesics. This effect is also obtainable in human patients and is utilized in combined anæsthesia aud for analgesic purposes. C. may —possibly by virtue of its depressive effect upon temperature and metabolism counteract shock induced by bleeding or trauma in the rat.

PREVIOUS EXPERIENCE WITH CHLORPROMAZINE IN PSYCHIATRIC THERAPY

A few of the numerous publications on C. in the management of psychiatric patients will be reviewed below.

Delay and co-workers (1952) (7) appear to have been the first to use C. as the only medication for psychotic patients showing excitement and motor unrest. They have, moreover, given a detailed description of 8 manic patients (1952) (8). These authors use daily doses of 100 mg, beginning with intramuscular injections and later changing to oral administration. Although apparently, the manic state subsided in nearly all the patients within the first few days, relapses were the rule, unless the treatment was extended over 3 weeks. *Delay and associates* describe the effect of C. as follows: During the first days the patients show an increased need of sleep, but they can easily be awakened. They are drowsy, but can feed themselves. During the subsequent 2 or 3 days the hypnotic effect is far less marked, but the patients are in a neutral mood, not talking spontaneously and only answering questions with some hesitation. According to *Delay* "the patients appear to be sunk into a state of gentle indolence, as if segregated from their environment by an invisible wall." This rather dramatic description holds a grain of reality, confirmed by subsequent authors and often described as "chemical lobotomy".

The indications for treatment with C. have later been ever more extended. The best results are, however, still obtained in manic and hypomanic conditions as well as in various states of agitation and unrest (*Lehmann & Hanrahan*). Like other workers, *Chatagnon & Chanoit* (1953) (5) maintain that the ætiology of the psychomotor excitement is of fairly subordinate importance, good results being obtained in ex-

cited patients of various categories, except in a few whom they call impulsive schizophrenics. *Arnold, Hift & Solms* (1953) (3) as well as *Winkelman* (1954) (18) have obtained good results in confusional and senile agitated states. *Arnold et al.* also obtained improvement of confusion in epilepsy and following concussion of the brain. According to *Sizaret & Salomon* (1953) (16) delirium tremens may yield to a few injections of C.—The effect of C. upon depression is disputed, but improvement seems to be obtainable, where the depressive state has been characterized by anxiety, hypochondriac thoughts, or agitation (*Anton-Stephens* (1954) (2)). *Staehelin & Kielholz* (1953) (17) often obtain a good effect in psychoses with hallucinations and delusions. This leads us to the question regarding what can be expected from C. in schizophrenia. In this disease *Anton-Stephens* has obtained unmistakable suppression of the intensity of hallucinations. *Meyer* (1953) (14), who combined C. with sedatives, particularly of the barbituric acid group, succeeded in abolishing catatonic manifestations and in arresting stupor in schizophrenia. He also obtained improvement in about 50 % of paranoid schizophrenics. This improvement outlasted the period of administration which was 3 weeks. In hebephrenia he obtained distinct relaxation, better contact, and improvement of stereotyped behaviour, but the symptoms returned after the drug was withdrawn. Many other authors have observed a relaxing effect of C. in schizophrenics. According to *Winkelman* it is the usual response, whereas *Elkes & Elkes* (1954) (9) obtained this effect in some cases. In neuroses the value of C. is uncertain, the result being incalculable, even in apparently identical cases. Yet, *Sigwald & Bouttier* (1953) (15) as well as *Winkelman* maintain that particularly obsessional thoughts and hypochondriasis subside and anxiety and irritability decrease. In neuroses, C. has been used as a means of promoting contact in instituting psychotherapy (*Arnold, Hift & Solms*). In addition, it has been successfully used to mitigate withdrawal symptoms in cases of drug addiction (*Arnold, Hift & Solms* and *Staehelin & Kielholz*). Various publications also report on the good results of C. in combination with sedatives (*Meyer*), with E.C.T. (*Arnold, Hift & Solms*), and with insulin (*Lancaster & Jones* (1954) (12)). Several authors have obtained good results with C. on an out-patient basis, but others warn against using the drug without constant supervision.

The above-mentioned authors have employed various modifications of *Delay and his associates'* procedure. As a rule the intramuscular doses have ranged from 100 to 200 mg, the oral ones from 75 to 300 mg daily according to the category of patients. Recently, e.g. English workers (personal communication) have started using far higher doses

by mouth, e.g. 1 g daily. This is said to make for a more rapid onset of the effect, although there does not seem to be any parallelism between the size of the dose and the effect. Nothing has yet been published regarding the side effects of this massive dosage. Most authors start with intramuscular injections, but a few use tablets alone. The period of treatment has varied from a few days up to several months, depending i.a. on divergent views regarding the mode of action of this drug. These views range from the extremes of considering it ineffective if no effect has been obtained in one week to finding the effect at the end of 4–6 weeks or a full effect not even until the drug has been withdrawn.

To save space, the subsidiary effects ascribed to C. by previous authors will not be discussed here, as they correspond in all essentials to those observed in our series. The interested reader is referred to a detailed report by *Giacobini & Lassenius* (1954) (7) on complications occurring during the treatment with C. alone or combined with other sedatives.

THE AUTHOR'S EXPERIENCE WITH CHLORPROMAZINE ("LARGACTIL")[1] IN THE TREATMENT OF PSYCHOTIC PATIENTS

Material.

The *main series* from Department D comprises 30 female patients who have completed courses of C. 21 of them are schizophrenic; 1 of them has been lobotomized three times, 10 twice, 8 once, and only 2 have not undergone lobotomy. Thirteen of the 21 patients had received E.C.T. in the course of the past year, with only transitory effect in 11 and no effect in 2. Combined insulin shock and E.C.T. had not been used for the past few years. In the 8 cases operated upon once, the lobotomies had been carried out more than one year ago; this also applies to 7 of the re-lobotomized patients. Only in 3 of the re-lobotomized patients and in the one who had had three operations had the last operations been performed from 6 to 12 months before C. was instituted. Thirteen patients were hebephrenic, 5 paranoid, and 3 catatonic; of course, this grouping is with the usual reserve as regards sliding transitions. The diagnostic criteria were the classical ones of autism with lack of emotional contact, loss of contact with reality, auditory hallucinations, delusions, and stereotypy combined with the long observation period. Only 3 of the 21 patients had been ill for less than 10 years, and 9 between 20 and 30 years. The age distribution was

[1] Manufactured and generously supplied by Messrs. May & Baker, Dagenham, England.

from 32 to 70, more than half being about 40.—The remaining 9 patients, ranging in age from 16 to 77, suffered from: Manic-depressive psychosis with mania of 6 months' duration in the case of 2 patients and of 18 months' duration in the third, who was also senile. A fourth patient had arteriosclerotic dementia with confusion and stereotyped yelling for hours on end. The 5th patient had puerperal psychosis with fears and hallucinations as well as depressive features. The 6th case was first diagnosed as schizophrenia of 3 years' duration, but the striking effect of C. suggested that she must be suffering from episodic schizophreniform psychosis with pronounced psychogenic factors. Prior to C. therapy this patient alternated between autism with apathy, also towards a baby she had given birth to about six months previously, and belligerent destructive phases during which she appeared to have marked hallucinations. The 7th patient had episodic psychosis and was mentally retarded, and the last two patients exhibited marked behaviour disorders, also owing to mental retardation.

As already mentioned, the treatment was repeated in 3 of the schizophrenics after they had relapsed to the pre-treatment condition. In one of these cases the treatment was started with injections of physiological saline and placebo tablets.

To this material may be added a *supplementary series* of about 50 female patients who have been started on the treatment during the past 2 months and for whom only sparse control values are available. Most of them are schizophrenics, several of whom have not been lobotomized, but there are also several elderly, excited patients and a few others.

Procedure.

The treatment schedule will be briefly outlined below:

It was endeavoured to administer C. alone in order to be able to assess its effect. Exceptions were made in only 2 patients with convulsions who went on receiving antispasmodics. In addition, C. was administered for a period so long, 2 months (in 2 cases, however, only 1 month), that a lacking effect could not be attributed to too short a course of treatment. We realized the risk that the frequent tests involving more attention from the staff, might *per se* improve the patients' condition. In order to guard against this risk, we selected mainly patients who prior to the treatment had been in an unchanged, poor condition for months and who had been as unaffected by their environment as at all possible, and patients who had shown no or only transitory improvement by other treatments. Because of practical difficulties, we have not been able to carry through treatment with in-

different placebo tablets in more than one case, or to repeat the treatment at the same conditions in more than three.

In conducting the treatment, we have paid regard both to the publications from other countries on the use of C. in psychoses and to the practical possibilities in the department. Because of overcrowding, we could not isolate the patients, not even while initiating the treatment, as has been recommended by other workers. We also had to restrict ourselves to administering the drug in the daytime.

With the exception of 2 cases (2 elderly patients) we started the *treatment* with injections in order to obtain a more rapid sedative effect and because several patients refused oral medication. As a rule, the injections were continued for 5 days. At the outset, 4 injections of 25 mg were given at 4 hour intervals, but as the same effect seems to be obtainable with 2 injections of 50 mg at 8 hour intervals, we now inject at 7 a.m. and 3 p.m. during the first 2 or 3 days. During the last 2 or 3 days, when the sedative effect is decreasing, the patients often require injections of 50 mg also at 11 a.m. and occasionally also at 7 p.m. During the course of injections, the patients were kept in bed—with or without a belt according to the nature of the case — to counteract the risk of orthostatic drop in blood pressure. For practical reasons, the change to oral administration was not gradual. On the 6th day, when the patients got out of bed, they were given tablets in a dose corresponding to the intramuscular injections. Although the oral dose is only half as potent, this was done partly in order to avoid dizziness, when the patients got up and partly in order to be able to rise to and not miss a suitable maintenance dose. As a rule, the dosage was increased by only 1 tablet, i.e. 25 mg, at a few days' intervals, from 100 to a maximum of 300 mg daily. Psychotic patients often develop a certain tolerance, so that the dose may have to be increased, e.g. from 200 to 300 mg, during the latter period of treatment. More rarely, as reported from abroad especially in the treatment of neurotics, the dose may be lowered. In a few cases, the intramuscular injections were continued or resumed after the oral treatment had been started, either because the patients became excited during the latter period of intramuscular treatment or because at a later stage they became refractory to oral treatment. On the whole, however, it is not advisable to continue the injections too long, as they are apt to give rise to infiltrations. After 2 months' treatment, C. was gradually withdrawn in the course of 1 or 2 weeks, as sudden withdrawal is said to involve the risk of relapse. We have not, however, been able to confirm this finding in the few cases in which the drug was withdrawn abruptly.

Four times daily the pulse, blood pressure, temperature, and respi-

ration were *controlled*—during the 5 days of the injection therapy also 1½ hour after the injections at which time the clinical effect reaches a maximum. These values were compared with the corresponding values from the 3 pre-treatment days, although this is not a reliable basis of comparison owing to the patients' excitement before the treatment. For this reason, these determinations were continued for a month after treatment in 8 cases. In the case of patients not confined to bed, the determinations were made after a rest—often too short as a result of the patients' condition. For purposes of further control, the urine was examined for albumin, blood, pus, and sugar every week and complete blood studies as well as electrocardiograms made every 2 weeks. The weight was controlled monthly. Liver function tests were only performed in a few cases who exhibited symptoms of dyspepsia. The nursing staff recorded the results of the determinations each time and wrote daily notes on the patients. A weekly analysis was performed by the author.

Therapeutic Effect.

In evaluating the effect of treatment with C. the largest group, *schizophrenics,* will be considered separately. The results cannot be classified, as the effect of C. appears to be qualitatively uniform. Without doubt, there have been quantitative differences in effect. A grading of such differences was not performed, partly because it carried considerable sources of error and partly because it would have to be based on detailed reports of the histories which would exceed the scope of this paper. Improvement during treatment with C. is taken to mean an alteration in behaviour in a more peaceful direction, the patients being less excited and noisy and adapting themselves better to life in the department. As judged by this simple definition, improvement was obtained in 20 of the 21 schizophrenics. It must be added, however, that in two of these cases the improvement lasted for only two weeks in the course of or at the end of the treatment.

It is worth emphasizing that in the schizophrenics the average period before improvement became manifest was 3 weeks, ranging from a few days to 8 weeks. In 3 cases, improvement was most marked after the treatment had been completed. The effect often appears gradually in the course of 2 to 6 weeks.

To illustrate the practical value of the treatment, it may be mentioned that among 14 improved schizophrenics who completed the treatment from 6 to 2 months ago, only 2 relapsed at once, 1 at the end of one month, 2 at the end of two months, and 2 at the end of more than

four months. One has not yet relapsed four months after, and 6 have not relapsed three months after the treatment.

On the whole, our findings have confirmed the experience of previous authors on the effect of C. in excited schizophrenics. C. is above all pacifying. After the initial drowsiness, the calming effect manifests itself in less belligerence, less irritability, and far less impulsiveness. This effect is obtained without any reduction in initiative which is an invariable consequence of other sedatives. On the contrary, C. improves the autistic attitude; the patients become more accessible and begin to seek contact. They begin to dress spontaneously, become less incontinent, and take part in the work in and outside the department. Thus, a sort of resocialization takes place, although the patients have not undergone any form of conscious psychotherapy. Since apparently their hallucinations and other morbid ideas have faded and receded, the patients give an impression of being less tense and harassed. They are more kindly and show a more objective attitude towards their psychopathological phenomena, so that frequently they can be persuaded to discuss and describe them. Yet, some of the patients insist that the morbid ideas have only receded, not disappeared. With a kind smile they may contend that the drug does not help, although the objective improvement is unmistakable.

As regards the effect of C. on special signs it is worth mentioning, in addition to the marked effect on the hallucinatory phenomena, that in 2 typically automutilatory patients, the automutilations ceased. In one case catatonic manifestations subsided unmistakably. One patient, whose predominant symptom was hallucinations, could be discharged for later out-patient treatment.

The only patient who failed to show any effect of the treatment had been lobotomized and was suffering from stereotyped ideas of influence and organic sensations accompanied by constant outbursts of rage.

Lobotomized and re-lobotomized patients appear to respond in the same way.

In 6 of the 9 *non-schizophrenic patients* of the main series who showed improvement, the effect did not apart from the arteriosclerotic patient with bouts of yelling who was merely pacified—follow the schematic pattern seen in the schizophrenic group. I am not referring so much to the fact that 2 of the manic patients returned to their neutral phase as to the distinct improvement observed in the case of puerperal psychosis and in the other two of episodic psychoses. Before treatment, they were autistic, bewildered, harassed, and anxious and after the treatment the two latter patients appeared to be in

their habitual state and were discharged. True, the patient with puerperal psychosis became somewhat depressed during the treatment, but she was discharged at the request of her husband. In these 6 cases the improvement appeared within a few days. C. failed completely in 3 patients, including the one with mania of 6 months' duration. In this case subsequent treatment with lithium was beneficial. The two mentally retarded patients with behaviour disorders were also completely refractory to treatment with C. in doses of 300 mg daily.

Repeated treatment in the case of 3 schizophrenics under the same conditions gave very much the same effect as the first treatment, after the patients had relapsed to their former state. In one of these cases, the treatment was started with injections of physiological saline solution and continued with placebo tablets for a few weeks. During this period, her condition remained entirely unchanged, whereas it had improved during a corresponding period of the first treatment. No improvement occurred until C. had been started.

In 16 cases C. had a more prolonged and more marked effect than E.C.T. given during the past year, indicating that probably it is often beneficial in the treatment of severely excited patients.

Experience from treating *about 50 female patients* during the past 2 months with C. but exercising a less intense control has confirmed the pacifying and resocializing influence of C., also on non-lobotomized schizophrenics. This holds out the hope that perhaps lobotomy may be avoided in some cases. The results were on the whole good in excited, noisy, confused elderly patients. It is, moreover, worth stating that another patient with prolonged puerperal psychosis responded promptly, although combined treatment with insulin shock and E.C.T. had given only transitory results. Furthermore, a psychopathic individual with emotional lability and periods of dysphoria characterized by fears was considerably improved by a course of C., after which she was discharged.

During chlorpromazine therapy the patients nearly always sleep well. Their appetite is usually improved and half of them gain weight.

RESULTS OF CONTROL TESTS

A brief description will be given of the special effects of C. as elucidated by the results of the control tests.

The pulse rate increased in 80 % of the main series. The most marked acceleration, often up to 100 or 120, is observed in the early injection therapy, and later the rate is only about 10 above the pre-treatment level. On the whole, the pulse rate fluctuated only a little more than before treatment. We did not observe the marked excursions of between 60 and 140 reported from other countries, although

we have recorded about ten thousand values. In 2 of the 8 patients followed up for one month after treatment, the pulse remained frequent for 4 and 2 weeks, respectively. In only one of these 8 cases did the pulse rate show lower values than recorded before the treatment, although this might be expected considering that usually the patients were calmer after the treatment than during the 3 pre-treatment days.

Palpatory blood pressure was in 14 (almost half the cases) about 10–20 mm lower during the treatment. In another one-sixth a decrease down to 90 100 occurred during the initial injection therapy, in a few cases even down to 80 mm. Just as the pulse rate remained high, the blood pressure remained low—for 1 month and 10 days, respectively—in only 2 of the 8 cases followed up for one month after the treatment. No case of circulatory collapse occurred in connection with the treatment, but a few patients suddenly lay down in their beds one or two hours after the injections at which time the effect appears to have been maximal. Some patients also moved a little unsteadily at the commencement of oral therapy.

As far as pulse rate and blood pressure are concerned, only a certain parallelism was found between the dosage and the recorded alterations which in most cases subsided in the course of the treatment.

Temperature remained on the whole unchanged. Only in one case does it seem to have been continuously decreased during the entire course, not rising until C. was withdrawn. During the last days of the injection treatment and during the first few days after, 40 % exhibited rise of temperature, usually only up to 38° C., but in two cases up to 38.5 and 39.0° C., respectively. Only half of these patients had infiltrations at the site of injection as a possible explanation of this fever. Two patients had low-grade fever during the first 2 weeks of treatment, but both exhibited infiltrations. Three had brief episodes of fever about the 14th day and three after one month without demonstrable cause; this was therefore ascribed to the drug. It has been reported that by its depressive effect on the temperature C. may mask fever in the event of infections. We cannot confirm these findings. In the supplementary series there was one case of bronchopneumonia in which the temperature rose to 40° C.; the infection yielded to penicillin in a few days. Another patient with influenza ran a temperature of 39° C. and improved spontaneously without the treatment being interrupted.

Respiration remained unchanged in character and frequency.

Electrocardiography showed some tendency to flattening of the T waves, in one case with inversion of T_3. One patient exhibited marked extrasystoles, but without subjective complaints. This patient, whose electrocardiographic appearances were followed regularly, had also at other times shown extrasystoles.

Urinalyses failed to reveal albumin, blood, or sugar during the treatment. On one occasion pyuria occurred, but subsided after treatment with a sulpha drug. The daily output of urine was not measured, but it seems to have been somewhat increased.

Sedimentation rate increased in 7 cases, as a rule by about 10 mm, but in 2 cases from a slightly enhanced initial value to about 100 and then fell gradually during continued treatment. Six patients showed transitory and slight increase in the S.R. In 12 cases it remained unchanged, and in one it fell. In the case of 4 patients too few recordings were made to show the general trend.

Hæmoglobin concentration displayed a slight decrease in 4 and a transitory decrease in 6 cases, amounting to about 10 %. In 18 instances it remained un-

changed. In 2 cases the determinations of hæmoglobin are too few to give an idea of the tendency. The *colorimetric index* as well as the forms of red blood cells were normal throughout.

Differential counts, performed regularly in 28 cases, were normal throughout in 15. Five patients showed lymphocytic preponderance with more than 45 % mononuclears during the treatment and 6 showed a transitory shift towards lymphocytic preponderance, whereas in 2 patients showing this abnormality prior to the treatment, the counts were normalized during the treatment. Mild eosinophilia was a transitory phenomenon in 2 cases.

White cell counts, in the 26 cases in which they were regularly performed, displayed a decrease in 7 patients, marked in 2. In one of these cases the W.B.C. fell to below 3000, but on the following day it had again reached past 4000. In 12 instances the counts were unchanged. In 5 they varied widely, and in 2 they increased, transitorily in one. In the supplementary series a transitory drop to about 3000 occurred in 2 cases and a drop to between 2000 and 2500 of one week's duration in a patient who also developed exanthema. Finally, there was a case of agranulocytosis with counts as low as 600 cells. This case will, however, be discussed under subsidiary effects. It has been published in Ugeskrift for Læger 1954, No. 51.

It will be seen from what has been stated above that the control tests have on the whole only revealed certain tendencies, but no definite course, e.g. only a tendency to increased pulse rate and lowered blood pressure as well as to leukopenia. As mentioned above, however, the latter urges to caution.

SUBSIDIARY EFFECTS

The treatment was accompanied by certain complaints and subsidiary effects which will be described below.

In the main series the drug had to be withheld for a few days in 2 cases because of slightly itching exanthema, most pronounced in sites exposed to light. This rapidly subsided, and the treatment was resumed with slowly increasing doses. The intramuscular administration of C. is decidedly inconvenienced by the tendency to infiltrations, even if the sites of injection are rotated. Yet, all the injections were made into the gluteal muscles, and—in accordance with the warnings in the literature not into the thighs. By diluting the ordinary solution of 2½ % in 9 volumes of physiological saline, the frequency of the infiltrations was reduced by one half. In other words, they occurred in only one third of the cases. This also rendered the infiltrations softer and less tender. Three patients had convulsions; one of them for the first time after lobotomy 6 months previously; the second patient—with a history of regular seizures—had a few seizures during the early treatment; the third had a seizure on the 2nd day of treatment after having had none for 5 months. The two last-mentioned patients had been receiving their usual antispasmodic treatment. Incidentally, the subsidiary effects cannot be thoroughly elucidated, as the patients are usually unable to call attention to them, so only the objective signs can be reported. Fatigability at the commencement of the treatment was striking or reported by 10 of the 30 patients. Dizziness was noticed in 3 cases and a "far-away sensation" in 1. A tendency towards constipation was common, but was treated prophylactically with mild laxatives. Two patients had diarrhoea. One patient complained of dryness of the mouth, which has been repeatedly observed in the supplementary series; as a rule

boracic lincture affords some relief. One patient, stated to be allergic to various drugs to which she had reacted by menorrhagia, also had vaginal bleeding—but only slight—towards the end of the treatment. No other menstrual disturbances occurred.

In the supplementary series—where C. as a rule was administered by mouth from the commencement of treatment—the subsidiary effects were on the whole the same. In addition, a few patients had periocular oedema without subjective complaints. At an early stage one patient had exanthema which rapidly faded after C. was interrupted, but flared up when it was gradually resumed. The white cell counts were 2600 and 2100 immediately after and one week after C. was interrupted for the second time. Although the pre-treatment counts are unknown, it is reasonable to ascribe the low white cell counts as well as the exanthema to allergy to C. Recently, *Andersen* (1954 (1) has published two cases of prolonged, mild leukopenia following a short course of C. in low doses. In this connection it is worth returning to the case of agranulocytosis. The patient was a 71 year-old arteriosclerotic woman. After 6–7 weeks' treatment resulting in a good sedative effect of C. in increasing doses—300 mg daily during the last 12 days (a total of 10,600 mg)—she developed diarrhoea with marked fatigue and a temperature of about 39° C. The W.B.C. was 800 with only a few polynuclears. The patient was transferred to the medical department on the same day. On arrival there, the W.B.C. had dropped to 600. After blood transfusions, penicillin, and folic acid she recovered so much in one week that she was returned to our department. The W.B.C. was rapidly increasing, now again with preponderance of polynuclears. One week later, however, the patient contracted pneumonia; it was treated with aureomycin, but she succumbed within a few days. *Giocobini* & *Lassenius* have reported a case very like this one except that their patient had also been given phenergan (promethazine) and survived. A frequently reported complication is jaundice, usually of benign nature. *Grytting* (1954) (11), who has reported 2 cases, believes that it is due to intrahepatic occlusion as indicated by a biopsy specimen from one of his cases. Both Takata-Ara and thymol turbidity reactions were normal in these cases. We have had a case of jaundice in a 68 year-old schizophrenic who had been treated with C. for 4 weeks. During the past 14 days she had been receiving a relatively low dose, 150 mg daily. C. was withheld at once. The icterus index rose from 18 to 46 in the course of one week and then decreased to normal in a few weeks. The thymol turbidity reaction was negative, and there was no increase in urinary urobilinogen. There was no palpable enlargement of the liver, but mild pain, particularly below the right costal margin, and some anorexia, but the general condition was not affected. *Boardman* (1954) (4), however, has reported a fatal outcome of hepatic affection following administration of C. combined with a barbituric acid derivative to a 45 year-old woman with paranoid psychosis. This patient was, however, also suffering from mitral stenosis with signs of cardiac failure.

Having analysed the results of our control tests and the subsidiary effects during treatment with C., we direct our attention mainly to the clinical condition. Most emphasis is placed on jaundice, nausea, diarrhoea, exanthema, and marked fatigue. The last-mentioned signs indicate white blood counts which also should be performed regularly, e.g. once weekly, throughout the period of treatment. Differential

counts are performed only in the event of leukopenia. In our opinion, other blood studies afford no therapeutic guidance. This also applies to the ordinary liver function tests, so they are not used either. Since, moreover, the pulse rate, blood pressure, and temperature do not appear to yield information of much therapeutic value, we have abandoned the regular charting of these values. Owing to the frequency of infiltrations upon intramuscular injection, we try as far as possible to manage on oral administration alone, usually starting with 25 mg four times daily. By this route, the effect is somewhat slower in appearing, but dizziness is less marked, so that the patients need not be confined to bed, if only they rest frequently during the first few days. Injections are only used, if the patients refuse oral medication or if they have subsequently become refractory to oral administration. In such instances even small doses of parenteral C. may exert a pronounced effect.

CONCLUSION

Our experience with chlorpromazine in the treatment of excited psychotic patients has been so favourable in respect to its pacifying and resocializing effect that despite its subsidiary effects—especially the risk of agranulocytosis and hepatic affection—we feel that its therapeutic application ought to be extended.

In cases of mania, where chlorpromazine first proved its value, it is still indicated. Furthermore, we intend to use it in the treatment of excited, fearful, and harassed schizophrenics, especially in cases where hallucinatory phenomena predominate. Chlorpromazine opens up the possibility of avoiding E.C.T. and perhaps also lobotomy in some cases. It is also worth trying in cases of psychomotor excitement involving noisy behaviour and belligerence in confusional senile states.

It is true that our series is small, but the results were so surprisingly good that we are planning to extend the use of the drug to other forms of psychosis with varying psychogenic features, e.g. episodic psychoses and puerperal psychoses, in order to widen our favourable experience in this field. In addition, it is no doubt worth investigating the possibility of including in the range of indications cases of dysphoria in psychopaths and of behaviour disorders in mentally retarded subjects, although the treatment failed in two of our cases.

During treatment with chlorpromazine, the clinical condition must be supervised and white blood counts made at regular intervals.

SUMMARY

Thirty female psychiatric patients were treated with chlorpromazine (Largactil) for 2 months except for two who were treated for 1 month. All were constantly controlled with respect to pulse rate, blood pressure, temperature, and respiration and also underwent regular studies of electrocardiogram, urine, and weight as well as complete blood counts.

A good pacifying and resocializing effect was obtained in 20 out of 21 schizophrenics, 19 of whom had been lobotomized, 11 more than once. The favourable effect upon hallucinations is emphasized.

Out of the remaining 9 patients marked improvement was noted in 2 with mania, in 2 with episodic psychoses, in 1 with puerperal psychosis, and in 1 senile patient with arteriosclerosis and bouts of yelling. In 1 manic patient and in 2 mentally retarded patients with behaviour disorders no improvement was obtained.

Several of the patients who responded to chlorpromazine had proved almost quite refractory to E.C.T.

In a supplementary series of about 50 female psychiatric patients the favourable effects of chlorpromazine were confirmed, also in non-lobotomized schizophrenics.

In the main series, the treatment was initiated with intramuscular injections, whereas in the supplementary series chlorpromazine was usually administered only by mouth in order to avoid infiltrations. The maximum dose was 300 mg. daily.

As for subsidiary effects, the author emphasizes liver damage, which escapes detection by the ordinary function tests, and leukopenia increasing to agranulocytosis. During the entire treatment it is advisable to exercise an accurate clinical control and to perform regular leukocyte counts.

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PLASMA FIBRINOGEN IN CHRONIC NEUROLOGICAL DISEASES, WITH SPECIAL REFERENCE TO DISSEMINATED SCLEROSIS

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INTRODUCTION

The purpose of this paper is to ascertain how much importance can be attached to the previously demonstrated tendency towards increase in the plasma fibrinogen in disseminated sclerosis (*Persson*, 1952) with regard to its pathogenesis. Especially an attempt has been made to throw light on the question whether this raised fibrinogen is specific to disseminated sclerosis.

On the basis of a series of pathological-anatomical and experimental investigations *Putnam* (1936, 1937, 1937) believed having shown it to be probable that vascular damage or thrombi in the small veins in the central nervous system are responsible for the characteristic plaques in disseminated sclerosis.

Much work has been done to verify this theory, the result being that the original theory has been somewhat modified. Thus through thorough pathological-anatomical investigations *Broman* (1949) and *Haarr* (1949) were unable to demonstrate coagulation thrombi in multiple sclerosis, but defined disseminated sclerosis as a periphlebitis. *Fog* (1948) was also unable through his investigations to demonstrate thrombi, but he was able to show that plaques of the spinal cord medulla occur in connexion with the veins. Therefore these investigations have offered no proof that there are coagulation thrombi in the central nervous system, which might produce the characteristic plaques. In this field, investigations of recent years have shown that the thrombocytes alone are able to agglutinate and so block the vessels, which means that in human pathology thombi cannot be identified with

coagulation thombi. (*Copley* and *Houlihan*, 1947; *Singer, Bornstein* and *Wile*, 1947; *Hirsch, Favre-Gilly* and *Dameshek*, 1950).

Earlier investigations into disseminated sclerosis have shown that in this disease factors which can facilitate thrombus formation are demonstrable. Among other things it is known that if the content of fibrinogen and globulin in the plasma is increased, the electrical charge of the thrombocytes is reduced, which is indicated by an increased agglutinability (*Roskam*, 1926). As mentioned above, an increase of plasma fibrinogen has been found in many cases of disseminated sclerosis; this led to the assumption that in this disease there is an increased tendency towards the formation of emboli, which might produce the characteristic plaques. In order to decide whether the raised fibrinogen demonstrated could possibly play a part in the pathogenesis of the disease, it was considered of importance to in-

Average for plasma fibrinogen.

	Disseminated sclerosis	Chronic epidemic encephalitis	Other chronic neurological diseases	Chronic non-neurological diseases	Healthy persons
	256	408	542	589	414
	544	581	257	381	297
	360	292	556	417	319
	362	453	283	298	502
	519	282	476	619	425
	457	411	408	524	461
	410	518	352	502	306
	348	683	406	364	487
	555	360	521	457	342
	425	598	577	309	489
	496	485	557	517	470
	260	529	276	579	379
Men	453	279	445	502	294
	404	356	361	315	435
	482	504	536	428	493
	435	476	325	529	409
	391	408	434	391	360
	517	489	240	490	409
	344	517	305	709	340
	415	460	474	574	243
	362	488	572	687	368
	539	396	356	317	457
	473	436	483	469	499
	641	372	366	520	303
	454	498	514	638	476

	Disseminated sclerosis	Chronic epidemic encephalitis	Other chronic neurological diseases	Chronic non-neurological diseases	Healthy persons
	213	429	360	487	468
	423	277	434	534	505
	440	453	314	512	388
	517	372	584	368	397
	480	605	318	462	412
	390	464	602	387	433
	432	550	381	506	380
	638	438	497	451	456
	503	546	445	621	482
	477	435	518	507	470
	621	547	431	477	399
	408	399	379	580	455
Women ...	437	428	521	699	384
	390	510	442	519	370
	539	491	303	670	452
	479	506	531	712	446
	356	443	435	388	374
	494	537	526	589	218
	370	492	410	624	467
	461	635	524	398	372
	612	343	405	672	414
	578	457	457	584	407
	423	653	488	427	381
	385	466	507	376	457
	476	474	411	489	389
Average for men	440	451	425	485	399
Average for women	461	478	449	521	415
Average for both groups	451	465	437	503	407

vestigate the plasma fibrinogen, partly in some closely related diseases, partly in other chronic neurological diseases, and also in non-neurological but chronic diseases.

THE CLINICAL MATERIAL, EXPERIMENTAL TECHNIQUE, AND RESULTS OF EXPERIMENTS

The patients from whom plasma fibrinogen estiminations were made, were divided into the following four groups, each comprising 50 patients: (1) disseminated sclerosis, (2) chronic epidemic encephal-

itis, (3) other chronic neurological diseases (cerebrospinal syphilis, cerebral haemorrhage), and (4) other chronic non-neurological diseases (polyarthritis and chronic bronchitis). The plasma fibrinogen was also estimated in (5) 50 normal persons.

As it has been shown that the plasma fibrinogen content increases with age (*Lasch*, 1932), the patients have been selected so that their ages are between 30–50 years.

However, there is a correlation between the fibrinogen content of plasma and the sedimentation rate (*Fahraeus*, 1921), i.e. the more the sedimentation rate rises, the greater is the fibrinogen content. Therefore, in order to compare the various groups, the patients were selected in such a way that their sedimentation rates were not above 15 mm/hr.

The blood tests were taken at the same time of day, the patients having fasted for 15 hours. The plasma fibrinogen was estimated according to the technique of H. C. Gram.

The results of experiments are given in the table (the results in patients suffering from disseminated sclerosis are the average of a number of determinations).

DISCUSSION

As shown in the table, there is a rise of the plasma fibrinogen not only in disseminated sclerosis but also in chronic epidemic encephalitis. This sometimes produces a picture strikingly similar to that of disseminated sclerosis. Moreover, it is seen that there is also a rise of the fibrinogen in other chronic neurological diseases as well as in non-neurological but chronic diseases of degenerative or inflammatory nature. This last finding is corroborated by the results of the investigations of *Ham* and *Curtis* (1938). In all cases the fibrinogen content is found to be higher in women. This means that the raised plasma fibrinogen of disseminated sclerosis is not a characteristic of this disease as compared with many other chronic diseases.

Consequently the demonstrated increase of fibrinogen in disseminated sclerosis can apparently only be accredited with importance if in connection with the disease special conditions are found which come to give a raised fibrinogen content special importance. As stated above, a rise in plasma fibrinogen is known to occur at thrombotic conditions and it is possible that the plaques of disseminated sclerosis are produced by emboli which block the vessels thus producing infarcts.

Previous investigations (*Persson*, 1953) have shown that there is a tendency towards a rise in the fibrinogen during the exacerbations of disseminated sclerosis, whereas it was also found that there may

be a rise in the plasma fibrinogen content not accompanied by an exacerbation. The reason for this may be that possible thrombi remained in "silent zones". or that they have been too small to produce symptoms; but the most likely explanation is perhaps that the raised fibrinogen content has not given rise to the formation of new thrombi at all.

If the reason for thrombus formation should be the increased fibrinogen, one would, moreover, expect to find signs of thrombi in other sites, but in disseminated sclerosis signs of thrombus formation are almost only found in the central nervous system, and the symptoms, at least, are from there only. Admittedly this fact might be due to the special structure of the venous plexuses in the central nervous system (*Fog*, 1948), which are such that in no other place in the body will a small thrombus produce such serious symptoms. The special character of the structure of the central nervous system, however, offers no explanation why an increase of fibrinogen should be of special significance in the pathogenesis of disseminated sclerosis, since this rise is not specific to disseminated sclerosis. On the contrary a greater increase is seen in other neurological diseases, without the finding on this account of an increased tendency towards thrombus formation in these diseases.

The pathological-anatomical picture in disseminated sclerosis shows that, apart from being dependent on the vascular system, the localization of plaques depends upon the distance from the cerebrospinal fluid. In this respect periventricular sclerosis is very typical (*Hallervorden*, 1940). This fact suggests an interaction between the blood and the cerebrospinal fluid in the formation of plaques. The actual provoking factor is perhaps to be found in the cerebrospinal fluid, the increased fibrinogen content of the plasma being presumably only an accompanying phenomenon.

SUMMARY

On the basis of pathological-anatomical investigations *Putnam* has advanced the hypothesis that thrombi in the central nervous system produce the characteristic plaques in disseminated sclerosis. A rise in the plasma fibrinogen content facilitates thrombus formation. It has been shown in an earlier study that a rise in the plasma fibrinogen often occurs in disseminated sclerosis. However, the investigations described here seem to show that this rise is not specific to disseminated sclerosis. In fact a greater rise in the fibrinogen content may occur in other neurological diseases without a tendency to throm-

bus formation. Therefore the raised plasma fibrinogen content should probably rather be regarded as a sign accompanying the actual cause of the disease.

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